

## ? logon

\*\*\* It is now 2009/09/01 07:35:04 \*\*\*  
(Dialog time 2009/09/01 06:35:04)

### Preferences:

1. Default save option: [HTML]
2. Graphic Images.
  - Maximum width in pixels : [300]
  - Maximum height in pixels: [300]
3. Hold output position (don't scroll to the output buffer end): [Yes]
4. Command separators (add HR after every command): [No]
5. Type separators (add HR after every record): [Yes]
6. Linking Pane: [Right]
7. Status location.
  - Below Type ahead buffer : [Yes]
  - In Browser status line: [No]
8. Show Estimated Cost Summary: [Yes]
9. Highlight Search Terms: [No]
10. Display Detailed Results by Search Term: [Yes]
11. Show Results by File (multifile search): [Yes]
12. Display Postings: [No]
14. Expand Items: 10
15. Hold Expand output position (don't scroll to the output buffer end): [Yes]
16. KWIC Window: 30
17. Output Cost Notification: [No]
18. Prompt for Subaccount at Logon: [No]
19. Hide History Tab: [No]
20. Show Preferences at Login: [Yes]
21. Show hyphen(s) in display set command : [Yes]

**Please enter a command or be logged off in 5 minutes**

## ? b 155 biosci medicine 399

```
01sep09 05:56:04 User276629 Session D275.1
      $0.00      0.253 DialUnits File415
$0.00 Estimated cost File415
$2.93 INTERNET
$2.93 Estimated cost this search
$2.93 Estimated total session cost      0.253 DialUnits
```

```
SYSTEM:OS - DIALOG OneSearch
File 155:MEDLINE(R) 1950-2009/Aug 28
      (c) format only 2009 Dialog
File 5:Biosis Previews(R) 1926-2009/Aug W5
      (c) 2009 The Thomson Corporation
File 24:CSA Life Sciences Abstracts 1966-2009/Sep
      (c) 2009 CSA.
File 28:Oceanic Abstracts 1966-2009/Sep
      (c) 2009 CSA.
```

File 34:SciSearch(R) Cited Ref Sci 1990-2009/Aug W4  
(c) 2009 The Thomson Corp

File 35:Dissertation Abs Online 1861-2009/Jul  
(c) 2009 ProQuest Info&Learning

File 40:Enviroline(R) 1975-2008/May  
(c) 2008 Congressional Information Service

\*File 40: This file is closed and will no longer update. For similar data, please search File 76-Environmental Sciences.

File 41:Pollution Abstracts 1966-2009/Sep  
(c) 2009 CSA.

File 44:Aquatic Science & Fisheries Abstracts 1966-2009/Sep  
(c) 2009 CSA.

File 45:EMCare 2009/Aug W4  
(c) 2009 Elsevier B.V.

File 50:CAB Abstracts 1972-2009/Aug W4  
(c) 2009 CAB International

File 65:Inside Conferences 1993-2009/Aug 28  
(c) 2009 BLDSC all rts. reserv.

File 71:ELSEVIER BIOBASE 1994-2009/Aug W5  
(c) 2009 Elsevier B.V.

\*File 71: The file has been reloaded. Accession numbers have changed.

File 72:EMBASE 1993-2009/Aug 27  
(c) 2009 Elsevier B.V.

\*File 72: EMBASE Classic (File 772) now open to all Dialog customers. See HELP NEWS 772 for information.

File 73:EMBASE 1974-2009/Aug 27  
(c) 2009 Elsevier B.V.

\*File 73: EMBASE Classic available to all Dialog customers. See HELP NEWS 772 for information.

File 76:Environmental Sciences 1966-2009/Sep  
(c) 2009 CSA.

File 91:MANTIS(TM) 1880-2009/Aug  
2001 (c) Action Potential

File 98:General Sci Abs 1984-2009/Sep  
(c) 2009 The HW Wilson Co.

File 110:WasteInfo 1974-2002/Jul  
(c) 2002 AEA Techn Env.

\*File 110: This file is closed (no updates)

File 135:NewsRx Weekly Reports 1995-2009/Aug W3  
(c) 2009 NewsRx

File 136:BioEngineering Abstracts 1966-2007/Jan  
(c) 2007 CSA.

\*File 136: This file is closed.

File 143:Biol. & Agric. Index 1983-2009/Aug  
(c) 2009 The HW Wilson Co

File 144:Pascal 1973-2009/Aug W5  
(c) 2009 INIST/CNRS

File 154:MEDLINE(R) 1990-2009/Aug 28  
(c) format only 2009 Dialog

File 164:Allied & Complementary Medicine 1984-2009/Aug  
(c) 2009 BLHCIS

File 172:EMBASE Alert 2009/Aug 28  
(c) 2009 Elsevier B.V.

File 185:Zoological Record Online(R) 1864-2009/Aug  
(c) 2009 The Thomson Corp.

File 357:Derwent Biotech Res. \_1982-2009/Jul W3

(c) 2009 Thomson Reuters  
 File 369:New Scientist 1994-2009/Aug W4  
 (c) 2009 Reed Business Information Ltd.  
 File 370:Science 1996-1999/Jul W3  
 (c) 1999 AAAS  
 \*File 370: This file is closed (no updates). Use File 47 for more current information.  
 File 391:Beilstein Database - Reactions 2008/Q2  
 (c) 2008 Beilstein GmbH  
 File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec  
 (c) 2006 The Thomson Corp  
 File 457:The Lancet 1992-2009/Aug W4  
 (c) 2009 Elsevier Limited.All rights res  
 File 467:ExtraMED(tm) 2000/Dec  
 (c) 2001 Informania Ltd.  
 File 138:Physical Education Index 1990-2009/Sep  
 (c) 2009 CSA.  
 File 149:TGG Health&Wellness DB(SM) 1976-2009/Aug W1  
 (c) 2009 Gale/Cengage  
 File 156:ToxFile 1965-2009/Aug W4  
 (c) format only 2009 Dialog  
 File 159:Cancerlit 1975-2002/Oct  
 (c) format only 2002 Dialog  
 File 162:Global Health 1983-2009/Aug W4  
 (c) 2009 CAB International  
 File 266:FEDRIP 2009/Jun  
 Comp & dist by NTIS, Intl Copyright All Rights Res  
 File 399:CA SEARCH(R) 1967-2009/UD=15110  
 (c) 2009 American Chemical Society  
 \*File 399: Use is subject to the terms of your user/customer agreement.  
 IPCR/8 classification codes now searchable as IC=. See HELP NEWSIPCR.  
 File 444:New England Journal of Med. 1985-2009/Aug W4  
 (c) 2009 Mass. Med. Soc.

Set	Items	Description
---	-----	-----

**? s (hemoglobin or haemoglobin)(n70)((red blood cell) or (red blood cells) or (RBC) or (RBCs))**

	656037	HEMOGLOBIN
	161088	HAEMOGLOBIN
	51992	RED BLOOD CELL
	30725	RED BLOOD CELLS
	107703	RBC
	44011	RBCS
S1	20344	(HEMOGLOBIN OR HAEMOGLOBIN) (N70) ((RED BLOOD CELL) OR (RED BLOOD CELLS) OR (RBC) OR (RBCS))

**? s s1(n60)(lysis or lyse)**

	20344	S1
	289265	LYSIS
	40987	LYSE

S2 357 S1(N60) (LYSIS OR LYSE)

? s s2(n70)(freeze or frozen or (-80))

357 S2  
257152 FREEZE  
445425 FROZEN  
0 -80  
S3 0 S2(N70) (FREEZE OR FROZEN OR (-80))

? s s2 and (FREEZE OR FROZEN OR (-80))

357 S2  
257152 FREEZE  
445425 FROZEN  
0 -80  
S4 1 S2 AND (FREEZE OR FROZEN OR (-80))

? t s4/medium/1

4/3/1 (Item 1 from file: 149)

DIALOG(R)File 149: TGG Health&Wellness DB(SM)

(c) 2009 Gale/Cengage. All rights reserved.

03048391 **Supplier Number:** 154512998 (USE FORMAT 7 OR 9 FOR FULL TEXT )

**Comparison of erythrocyte osmotic fragility among amphibians, reptiles, birds and mammals.**

Aldrich, Kevin J.; Saunders, David K.; Sievert, Lynnette M.; Sievert, Greg

Transactions of the Kansas Academy of Science , 109 , 3-4 , 149(10)

Fall ,

2006

**Publication Format:** Magazine/Journal

ISSN: 0022-8443

**Language:** English

**Record Type:** Fulltext **Target Audience:** Academic

**Word Count:** 4273 **Line Count:** 00404

**Descriptors:** Erythrocyte disorders--Research; Amphibians--Physiological aspects; Amphibians--Environmental aspects; Amphibians--Research; Reptiles-- Physiological aspects; Reptiles--Environmental aspects; Reptiles--Research

**Geographic Codes/Names:** 1U4KS Kansas

**Event Codes/Names:** 310 Science & research

? s ((red blood cell) or (red blood cells) or (RBC) or (RBCs))(n70)(lyse or lysis)(n70)(freeze or frozen or (-80))

51992 RED BLOOD CELL

```

30725 RED BLOOD CELLS
107703 RBC
44011 RBCS
40987 LYSE
289265 LYSIS
257152 FREEZE
445425 FROZEN
0 -80
S5 17 ((RED BLOOD CELL) OR (RED BLOOD CELLS) OR (RBC) OR
(RBCS)) (N70) (LYSE OR LYSIS) (N70) (FREEZE OR FROZEN OR
(-80))

```

**? s ((red blood cell) or (red blood cells) or (RBC) or (RBCs))(n70)(lyse or lysis or rupture or break)(n70)(freeze or frozen or (-80))**

```

51992 RED BLOOD CELL
30725 RED BLOOD CELLS
107703 RBC
44011 RBCS
40987 LYSE
289265 LYSIS
562862 RUPTURE
328305 BREAK
257152 FREEZE
445425 FROZEN
0 -80
S6 46 ((RED BLOOD CELL) OR (RED BLOOD CELLS) OR (RBC) OR
(RBCS)) (N70) (LYSE OR LYSIS OR RUPTURE OR
BREAK) (N70) (FREEZE OR FROZEN OR (-80))

```

**? rd**

>>>Duplicate detection is not supported for File 391.

>>>Records from unsupported files will be retained in the RD set.

```

S7 17 RD (unique items)

```

**? s s7 and (hemoglobin or haemoglobin)**

```

17 S7
656037 HEMOGLOBIN
161088 HAEMOGLOBIN
S8 1 S7 AND (HEMOGLOBIN OR HAEMOGLOBIN)

```

**? t s8/medium/1**

Dialog eLink: 

8/3/1 (Item 1 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

09291596 **PMID:** 2799892

**Paroxysmal nocturnal hemoglobinuria and the transfusion of washed red cells. A**

**myth revisited.**

Brecher M E; Taswell H F

Blood Bank and Transfusion Services, Mayo Clinic, Rochester, Minnesota.

Transfusion ( UNITED STATES ) Oct 1989 , 29 (8) p681-5 , ISSN: 0041-1132--Print

**Journal Code:** 0417360

Publishing Model Print

**Document type:** Journal Article

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

? s s7 not s8

	17	S7	
	1	S8	
S9	16	S7 NOT S8	

? t s9/medium/all

**Dialog eLink:** [USPTO Full Text Retrieval Options](#)

9/3/1 (Item 1 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

17782315 **PMID:** 17381616

**Proactive administration of platelets and plasma for patients with a ruptured abdominal aortic aneurysm: evaluating a change in transfusion practice.**

Johansson Par I; Stensballe Jakob; Rosenberg Iben; Hilslov Tanja L; Jorgensen Lisbeth; Secher Niels H

Department of Clinical Immunology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. p.johansson@post.tele.dk

Transfusion ( United States ) Apr 2007 , 47 (4) p593-8 , ISSN: 0041-1132--Print

**Journal Code:** 0417360

Publishing Model Print

**Document type:** Clinical Trial; Comparative Study; Journal Article; Research Support, Non-U.S. Gov't

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

---

**Dialog eLink:** [USPTO Full Text Retrieval Options](#)

9/3/2 (Item 2 from file: 155)

DIALOG(R)File 155: MEDLINE(R)  
(c) format only 2009 Dialog. All rights reserved.

16921294 **PMID:** 16371045

**Delayed and acute hemolytic transfusion reactions resulting from red cell antibodies and red cell-reactive HLA antibodies.**

Takeuchi Chikako; Ohto Hitoshi; Miura Saori; Yasuda Hiroyasu; Ono Satoshi; Ogata Takashi

Division of Blood Transfusion and Transplantation Immunology, Fukushima Medical University School of Medicine, Fukushima, Japan.

Transfusion ( United States ) Dec 2005 , 45 (12) p1925-9 , **ISSN:** 0041-1132--Print

**Journal Code:** 0417360

Publishing Model Print

**Document type:** Case Reports; Journal Article

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

---

**Dialog eLink:** [ISPTO Full Text Retrieval Options](#)

9/3/3 (Item 3 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

13516934 **PMID:** 10429773

**[Cost analysis of autologous transfusion methods--a study of 5,017 patients]**

Kostenanalyse autologer Transfusionsverfahren--eine Untersuchung bei 5017 Patienten.

Singbartl G; Schleinzer W

ENDO-Klinik Hamburg.

Anesthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie - AINS (

GERMANY ) Jun 1999 , 34 (6) p350-8 , **ISSN:** 0939-2661--Print **Journal Code:**

9109478

Publishing Model Print

**Document type:** Clinical Trial; English Abstract; Journal Article

**Languages:** GERMAN

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

---

**Dialog eLink:** [ISPTO Full Text Retrieval Options](#)

9/3/4 (Item 4 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

07650432 **PMID:** 6519067

**Filipin as a cholesterol probe. II. Filipin-cholesterol interaction in red blood cell membranes.**

Behnke O; Tranum-Jensen J; van Deurs B

European journal of cell biology ( GERMANY, WEST ) Nov 1984 , 35 (2) p200-15 ,

**ISSN:** 0171-9335--Print **Journal Code:** 7906240

Publishing Model Print

**Document type:** Journal Article

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

---

**Dialog eLink:** [USPTO Full Text Retrieval Options](#)

9/3/5 (Item 5 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

05314798 **PMID:** 954179

**Effect of different lysing and washing methods on free amino acid concentrations of sheep whole blood and erythrocytes.**

Wolfrom G W; Asplund J M

Clinical biochemistry ( CANADA ) Aug 1976 , 9 (4) p180-3 , **ISSN:** 0009-9120--

Print **Journal Code:** 0133660

Publishing Model Print

**Document type:** Comparative Study; Journal Article

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

---

**Dialog eLink:** [USPTO Full Text Retrieval Options](#)

9/3/6 (Item 1 from file: 5)

DIALOG(R)File 5: Biosis Previews(R)

(c) 2009 The Thomson Corporation. All rights reserved.

0019597965 **Biosis No.:** 200700257706

**Random healthy donor sera show varying effectiveness in hemolyzing ABO incompatible red blood cells.**



**Author:** Dumont Larry J (Reprint); AuBuchon James P; Herschel Louise; Roger Jill; White Thayer; Stassinopoulos Adonis  
**Author Address:** Dartmouth Hitchcock Med Ctr, Lebanon, NH 03766 USA\*\*USA  
**Journal:** Blood 108 ( 11, Part 1 ): p 286A NOV 16 2006 2006  
**Conference/Meeting:** 48th Annual Meeting of the American-Society-of-Hematology  
Orlando, FL, USA December 09 -12, 2006; 20061209  
**Sponsor:** Amer Soc Hematol  
**ISSN:** 0006-4971  
**Document Type:** Meeting; Meeting Poster  
**Record Type:** Abstract  
**Language:** English

---

**Dialog eLink:** [ISPTO Full Text Retrieval Options](#)  
9/3/7 (Item 2 from file: 5)  
DIALOG(R)File 5: Biosis Previews(R)  
(c) 2009 The Thomson Corporation. All rights reserved.

18626588 **Biosis No.:** 200510321088  
**Glycerol permeability and aquaporins from a freeze-tolerant amphibian that accumulates glycerol**

**Author:** Goldstein David L (Reprint); Frisbie James; Krane Carissa  
**Author Address:** Wright State Univ, Dayton, OH 45435 USA\*\*USA  
**Journal:** FASEB Journal 19 ( 5, Suppl. S, Part 2 ): p A1585 MAR 7 2005 2005  
**Conference/Meeting:** Experimental Biology 2005 Meeting/35th International Congress of Physiological Sciences San Diego, CA, USA March 31 -April 06, 2005; 20050331  
**Sponsor:** Amer Assoc Anatomists  
Amer Assoc Immunologists  
Amer Physiol Soc  
Amer Soc Biochem & Mol Biol  
Amer Soc Investigat Pathol  
Amer Soc Nutr Sci  
Amer Soc Pharmacol & Expt Therapeut  
Int Union Physiol Sci  
**ISSN:** 0892-6638  
**Document Type:** Meeting; Meeting Abstract  
**Record Type:** Abstract  
**Language:** English

---

**Dialog eLink:** [ISPTO Full Text Retrieval Options](#)  
9/3/8 (Item 3 from file: 5)  
DIALOG(R)File 5: Biosis Previews(R)

(c) 2009 The Thomson Corporation. All rights reserved.

16668160 **Biosis No.:** 200200261671

**Ex vivo expansion of CB cells without CD34 selection using co-culture on MSC**

**Author:** McNiece Ian K (Reprint); Harrington Jenny A (Reprint); James Rohaizah I (Reprint); Shpall Elizabeth J (Reprint); Mackay Alistair; Smith Alan

**Author Address:** Experimental Hematology, University of Colorado Health Sciences Center, Denver, CO, USA\*\*USA

**Journal:** Blood 98 ( 11 Part 1 ): p 851a-852a November 16, 2001 2001

**Medium:** print

**Conference/Meeting:** 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001; 20011207

**Sponsor:** American Society of Hematology

**ISSN:** 0006-4971

**Document Type:** Meeting; Meeting Abstract

**Record Type:** Abstract

**Language:** English

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**Dialog eLink:**

**USPTO Full Text Retrieval Options**

9/3/9 (Item 4 from file: 5)

DIALOG(R)File 5: Biosis Previews(R)

(c) 2009 The Thomson Corporation. All rights reserved.

09557459 **Biosis No.:** 198987005350

**DISCREPANCIES IN REVERSE ABO TYPING DUE TO PROZONE HOW SAFE IS THE IMMEDIATE-SPIN CROSSMATCH?**

**Author:** JUDD W J (Reprint); STEINER E A; O'DONNELL D B; OBERMAN H A

**Author Address:** DEP PATHOL, UNIV MICH HOSP UH-2G332110054, 1500 E MEDICAL CENTER DR, ANN ARBOR, MICH 48109, USA\*\*USA

**Journal:** Transfusion (Bethesda) 28 ( 4 ): p 334-338 1988

**ISSN:** 0041-1132

**Document Type:** Article

**Record Type:** Abstract

**Language:** ENGLISH

---

**Dialog eLink:**

**USPTO Full Text Retrieval Options**

9/3/10 (Item 1 from file: 24)

DIALOG(R)File 24: CSA Life Sciences Abstracts

(c) 2009 CSA. All rights reserved.

0003640518 IP Accession No: 6569463

**IMMUNOHEMATOLOGY: Delayed and acute hemolytic transfusion reactions resulting from red cell antibodies and red cell-reactive HLA antibodies**

Takeuchi, Chikako; Ohto, Hitoshi; Miura, Saori; Yasuda, Hiroyasu; Ono, Satoshi; Ogata, Takashi Division of Blood Transfusion and Transplantation Immunology, Fukushima Medical University School of Medicine, Fukushima, Japan, [mailto:hit-ohto@fmu.ac.jp] Transfusion , v 45 , n 12 , p 1925-1929 , December 2005

**Publication Date:** 2005

**Publisher:** Blackwell Publishing Ltd., 9600 Garsington Road Oxford OX4 2DQ UK, [URL:http://www.blackwellpublishing.com]

**Document Type:** Journal Article

**Record Type:** Abstract

**Language:** English

**Summary Language:** English

**ISSN:** 0041-1132

**Electronic Issn:** 15372995

**File Segment:** Immunology Abstracts

---

**Dialog eLink:**

**USPTO Full Text Retrieval Options**

9/3/11 (Item 2 from file: 24)

DIALOG(R)File 24: CSA Life Sciences Abstracts

(c) 2009 CSA. All rights reserved.

0003326796 IP Accession No: 8219853

**Novel nanoporous membranes from regenerated bacterial cellulose**

Phisalaphong, Muenduen; Suwanmajo, Thapanar; Sangtherapitikul, Preecha Department of Chemical Engineering, Chulalongkorn University, Bangkok 10330, Thailand, [mailto:muenduen.p@chula.ac.th]

Journal of Applied Polymer Science , v 107 , n 1 , p 292-299 , January 2008

**Publication Date:** 2008

**Publisher:** John Wiley & Sons, Baffins Lane Chichester W. Sussex PO19 1UD UK, [mailto:customer@wiley.co.uk], [URL:http://www.wiley.com/]

**Document Type:** Journal Article

**Record Type:** Abstract

**Language:** English

**Summary Language:** English

**ISSN:** 0021-8995

**Electronic Issn:** 1097-4628

**File Segment:** Bacteriology Abstracts (Microbiology B)

---

Dialog eLink:

USPTO Full Text Retrieval Options

9/3/12 (Item 1 from file: 34)

DIALOG(R)File 34: SciSearch(R) Cited Ref Sci

(c) 2009 The Thomson Corp. All rights reserved.

07842356 **Genuine Article#:** 214PH **No. References:** 26

**Cost analysis of autologous transfusion methods - A study on 5,017 patients**

**Author:** Singbartl G (REPRINT) ; Schleinzer W

**Corporate Source:** AIT ENDO KLIN HAMBURG,HOLSTENSTR 2/D-22767  
HAMBURG//GERMANY/ (REPRINT); NEUE PREGAMON KRANKENHAUS  
MANAGEMENT GMBH,/HEILBRONN//GERMANY/; SCHWIEZER  
PARAPLEGISCHES ZENTRUM,/NOTTWIL//GERMANY/

**Journal:** ANASTHESIOLOGIE INTENSIVMEDIZIN NOTFALLMEDIZIN  
SCHMERZTHERAPIE , 1999 , V 34 , N6 ( JUN ) , P 350-358

**ISSN:** 0939-2661 **Publication date:** 19990600

**Publisher:** GEORG THIEME VERLAG , P O BOX 30 11 20, D-70451 STUTTGART,  
GERMANY

**Language:** German **Document Type:** ARTICLE ( ABSTRACT AVAILABLE )

---

9/3/13 (Item 1 from file: 45)

DIALOG(R)File 45: EMCare

(c) 2009 Elsevier B.V. All rights reserved.

0003609607 **EMCARE No:** 29329593

**Cost analysis of autologous transfusion methods - A study on 5,017 patients**

Kostenanalyse autologer Transfusionsverfahren - Eine Untersuchung bei 5017 Patienten  
Singbartl C.; Schleinzer W.

**CORRESP. AUTHOR/AFFIL:** Singbartl G.: AIT - ENDO-Klinik Hamburg,  
Holstenstrasse 2, D-22767 Hamburg, Germany

Anesthesiologie Intensivmedizin Notfallmedizin Schmerztherapie ( Anesthesiol.  
Intensivmed. Nottf.med. Schmerzther. ) ( Germany ) June 1, 1999 , 34/6 (350-358)

**PUBLISHER:** Georg Thieme Verlag

**CODEN:** AISTE **ISSN:** 0939-2661

**DOI:** 10.1055/s-1999-8741

**Item Identifier (DOI):** [10.1055/s-1999-8741](https://doi.org/10.1055/s-1999-8741)

**DOCUMENT TYPE:** Journal ; Article **RECORD TYPE:** Abstract

**LANGUAGE:** German **SUMMARY LANGUAGE:** English; German

**NUMBER OF REFERENCES:** 26

---

9/3/14 (Item 1 from file: 135)  
DIALOG(R)File 135: NewsRx Weekly Reports  
(c) 2009 NewsRx. All rights reserved.

0000512556 (USE FORMAT 7 OR 9 FOR FULLTEXT)

**Reports from University of Copenhagen, Department of Clinical Immunology  
describe recent advances in abdominal aortic aneurysm therapy**  
Blood Weekly, May 10, 2007, p.54

DOCUMENT TYPE: Expanded Reporting  
LANGUAGE: English  
RECORD TYPE: FULLTEXT  
WORD COUNT: 392

---

9/3/15 (Item 1 from file: 149)  
DIALOG(R)File 149: TGG Health&Wellness DB(SM)  
(c) 2009 Gale/Cengage. All rights reserved.

03178181 **Supplier Number:** 160737822 (USE FORMAT 7 OR 9 FOR FULL TEXT  
)  
**Proactive administration of platelets and plasma for patients with a ruptured  
abdominal aortic aneurysm: evaluating a change in transfusion practice.(Author  
abstract)**

Johansson, Par I.; Stensballe, Jakob; Rosenberg, Iben; Hilslov, Tanja L.; Jorgensen,  
Lisbeth; Secher, Niels H.  
Transfusion , 47 , 4 , 593(6)  
April ,  
2007

**Document Type:** Author abstract **Publication Format:** Magazine/Journal  
ISSN: 0041-1132  
**Language:** English  
**Record Type:** Abstract **Target Audience:** Academic

**Descriptors:** Aneurysms

---

9/3/16 (Item 1 from file: 159)  
DIALOG(R)File 159: Cancerlit  
(c) format only 2002 Dialog. All rights reserved.

01052009 PMID: 75603457

**UPTAKE OF PROTEINS BY RED BLOOD CELLS.**

Rechsteiner

Dept. Biology, Univ. Utah, Salt Lake City, Utah 84112

Exp Cell Res

1975 ,

93 (2) p487-492 , ISSN 0014-4827

**Document Type:** JOURNAL ARTICLE

**Languages:** ENGLISH

**Main Citation Owner:** NOTNLM

**Record type:** Completed

? t s9/full/5

**Dialog eLink:**

USPTO Full Text Retrieval Options

9/9/5 (Item 5 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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05314798 PMID: 954179

**Effect of different lysing and washing methods on free amino acid concentrations of sheep whole blood and erythrocytes.**

Wolfrom G W; Asplund J M

Clinical biochemistry ( CANADA ) Aug 1976 , 9 (4) p180-3 , ISSN: 0009-9120--

Print **Journal Code:** 0133660

Publishing Model Print

**Document type:** Comparative Study; Journal Article

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

**Subfile:** INDEX MEDICUS

1. A study was conducted to determine the effect of different washing and lysing methods on the free amino acid concentrations of sheep erythrocytes (RBC) and whole blood. Methods of lysis included laking, freeze-thawing or sonication. RBC were washed with isotonic solutions of either saline or sucrose. 2. Washing the RBC with isotonic sucrose resulted in significantly greater concentrations for ten of the amino acids. Greater amino acid concentrations were realized when washed RBC were sonicated and when the RBC of whole blood were lysed by laking. 3. Suggestions are made for future application to whole blood and RBC amino acid determinations.

**Descriptors:** \*Amino Acids--blood--BL; \*Erythrocytes--analysis--AN ; Animals; Evaluation Studies as Topic; Hemolysis; Methods; Sheep

**CAS Registry No.:** 0 (Amino Acids)

**Record Date Created:** 19761101

**Record Date Completed: 19761101**

**? s (blood)(n70)(freeze or frozen or (freeze-thaw) or (-80))**

Processing

Processing

Processing

Processing

Processing

Processed 20 of 42 files ...

Processing

Completed processing all files

15437834 BLOOD

257152 FREEZE

445425 FROZEN

954 FREEZE-THAW

0 -80

S10 47705 (BLOOD) (N70) (FREEZE OR FROZEN OR (FREEZE-THAW) OR (-80))

**? s s10(n100)(hemoglobin or haemoglobin or Hb)**

47705 S10

656037 HEMOGLOBIN

161088 HAEMOGLOBIN

233636 HB

S11 2010 S10 (N100) (HEMOGLOBIN OR HAEMOGLOBIN OR HB)

**? s s10(n100)((hemoglobin or haemoglobin or Hb)(n50)(purif?))**

Processing

47705 S10

656037 HEMOGLOBIN

161088 HAEMOGLOBIN

233636 HB

4028171 PURIF?

S12 51 S10 (N100) ((HEMOGLOBIN OR HAEMOGLOBIN OR HB) (N50) (PURIF?))

**? rd**

>>>Duplicate detection is not supported for File 391.

>>>Records from unsupported files will be retained in the RD set.

S13 19 RD (unique items)

**? s s13/medium/all**

>>>Possible typing error near /

**? t s13/medium/all**

Dialog eLink: [USPTO Full Text Retrieval Options](#)

13/3/1 (Item 1 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

17948132 PMID: 17393480

**Raman microscopy of freeze-dried mouse eyeball-slice in conjunction with the "in vivo cryotechnique".**

Terada Nobuo; Ohno Nobuhiko; Saitoh Sei; Fujii Yasuhisa; Ohguro Hiroshi; Ohno Shinichi

Department of Anatomy, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Chuo-city, Yamanashi 409-3898, Japan.

nobuot@yamanashi.ac.jp

Microscopy research and technique ( United States ) Jul 2007 , 70 (7) p634-9 , ISSN: 1059-910X--Print **Journal Code:** 9203012

Publishing Model Print

**Document type:** Journal Article

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

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Dialog eLink: [USPTO Full Text Retrieval Options](#)

13/3/2 (Item 2 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

12318632 PMID: 9054405

**The globin-based free radical of ferryl hemoglobin is detected in normal human blood.**

Svistunenko D A; Patel R P; Voloshchenko S V; Wilson M T

Department of Biological and Chemical Sciences, Central Campus, University of Essex, Colchester, Essex CO4 3SQ, United Kingdom.

Journal of biological chemistry ( UNITED STATES ) Mar 14 1997 , 272 (11) p7114-21 , ISSN: 0021-9258--Print **Journal Code:** 2985121R

Publishing Model Print

**Document type:** Journal Article; Research Support, Non-U.S. Gov't

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

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Dialog eLink: [USPTO Full Text Retrieval Options](#)

13/3/3 (Item 3 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

11308907 **PMID:** 7994369

**Stabilized hemoglobin vesicles.**

Tsuchida E

Department of Polymer Chemistry, Waseda University, Tokyo, Japan.

Artificial cells, blood substitutes, and immobilization biotechnology ( UNITED STATES

) 1994 , 22 (3) p467-77 , **ISSN:** 1073-1199--Print **Journal Code:** 9431307

Publishing Model Print

**Document type:** In Vitro; Journal Article

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

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Dialog eLink: [USPTO Full Text Retrieval Options](#)

13/3/4 (Item 4 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

10533593 **PMID:** 1457926

**Characteristics of artificial red cells. Hemoglobin encapsulated in poly-lipid vesicles.**

Satoh T; Kobayashi K; Sekiguchi S; Tsuchida E

Tsukuba Research Laboratories, NOF Corporation, Japan.

ASAIO journal (American Society for Artificial Internal Organs - 1992) ( UNITED

STATES ) Jul-Sep 1992 , 38 (3) pM580-4 , **ISSN:** 1058-2916--Print **Journal Code:** 9204109

Publishing Model Print

**Document type:** In Vitro; Journal Article

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

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Dialog eLink: [USPTO Full Text Retrieval Options](#)

13/3/5 (Item 5 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

10049338 **PMID:** 1918801

**Preparation of unaltered hemoglobin from human placentas for possible use in blood substitutes.**

Fasan G; Grandgeorge M; Vigneron C; Dellacherie E

CNRS URA 494, ENSIC, Nancy, France.

Journal of biochemical and biophysical methods ( NETHERLANDS ) Jul-Aug 1991 , 23 (1) p53-66 , **ISSN:** 0165-022X--Print **Journal Code:** 7907378

Publishing Model Print

**Document type:** Journal Article

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

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**Dialog eLink:**

**USPTO Full Text Retrieval Options**

13/3/6 (Item 6 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

09774516 **PMID:** 2289306

**Polymerase chain reaction: amplification of DNA from fixed tissue.**

Crisan D; Cadoff E M; Mattson J C; Hartle K A

Department of Pathology, University of Pittsburgh, PA 15213-2582.

Clinical biochemistry ( CANADA ) Dec 1990 , 23 (6) p489-95 , **ISSN:** 0009-9120--Print **Journal Code:** 0133660

Publishing Model Print

**Document type:** Journal Article; Research Support, Non-U.S. Gov't

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

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**Dialog eLink:**

**USPTO Full Text Retrieval Options**

13/3/7 (Item 7 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

05307246 **PMID:** 951729

**Preparation of antihemophilic factor from indated plasma.**

Wickerhauser M

Transfusion ( UNITED STATES ) Jul-Aug 1976 , 16 (4) p345-50 , **ISSN:** 0041-1132-  
-Print **Journal Code:** 0417360

Publishing Model Print

**Document type:** Journal Article; Research Support, U.S. Gov't, Non-P.H.S.

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

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**Dialog eLink:** [ISPTD Full Text Retrieval Options](#)

13/3/8 (Item 8 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

04293564 **PMID:** 5005879

**Recent advances in the field of red cell structure.**

Baker R F

Pathobiology annual ( UNITED STATES ) 1971 , 1 p95-137 , **ISSN:** 0362-3025--

Print **Journal Code:** 1305471

Publishing Model Print

**Document type:** Journal Article; Review

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

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**Dialog eLink:** [ISPTD Full Text Retrieval Options](#)

13/3/9 (Item 1 from file: 50)

DIALOG(R)File 50: CAB Abstracts

(c) 2009 CAB International. All rights reserved.

0008083726 **CAB Accession Number:** 20013088268

**Gemobin - a new-generation natural biologically active food supplement.**

Chernyaev, S. I.; Lyublinskii, S. L.; Lyublinskaya, I. N.; Markov, M. V.

Dep. Sel'skogo Khozyaistva I Prodovol'stviya, Kaluga obl., Russia.

Pishchevaya Promyshlennost' ( 6 ): p.50-52

**Publication Year:** 2000

**ISSN:** 0235-2486

**Publisher:** OOO "Pishchepromizdat" Moscow , Russia

**Language:** Russian **Record Type:** Abstract

**Document Type:** Journal article

---

13/3/10 (Item 1 from file: 71)  
DIALOG(R)File 71: ELSEVIER BIOBASE  
(c) 2009 Elsevier B.V. All rights reserved.

0007196715      **Supplier Number:** 2007196786

**Raman microscopy of freeze-derived mouse eyeball-slice in conjunction with "in vivo cryotechnique"**

Terada N.; Ohno N.; Saitoh S.; Fujii Y.; Ohguro H.; Ohno S.

**Author Email:** nobuot@yamanashi.ac.jp

**Corresp. Author/Affil:** Terada N., Department of Anatomy, Interdisciplinary Graduate School of, Medicine and Engineering, University of Yamanashi, 1110 Shimokato, Chuo-city, Yamanashi 409-3898 , Japan

**Corresp. Author Email:** nobuot@yamanashi.ac.jp

Journal : Microscopy Research and Technique (Microsc. Res. Tech. ) , v70, n7, (634-639) , 2007 , United States

**Publication Date:** July 1, 2007 (20070701 )

**Coden:** MRTEE

**ISSN:** 1059-910X **eISSN:** 1097-0029

**Record Type:** Abstract; New

**Document Type:** Article

**Languages:** English      **Summary Languages:** English

**No. of References:** 20

**Descriptors:**

Freeze-drying; In vivo cryotechnique; Mapping; Raman microscopy; Raman spectrum

**Classification Code and Description:**

89 (CELL AND DEVELOPMENTAL BIOLOGY)

89.13 (METHODOLOGY)

89.13.1 (Techniques)

89.13.1.3 (Microscopy)

**Record History:** New; Created: July 20, 2007 (20070720 ) ; Delivered: June 22, 2008 (20080622 )

**Dialog Update Date:** 20081211; 08:07:19 EST

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**Dialog eLink:**

**USPTO Full Text Retrieval Options**

13/3/11 (Item 1 from file: 73)

DIALOG(R)File 73: EMBASE

(c) 2009 Elsevier B.V. All rights reserved.

0071381872      **EMBASE No:** 1979114101

**Analysis of iron content in individual human red blood cells by electron**

**microprobe and scanning electron microscope**

Davis D.

Donner Lab., Lawrence Berkeley Lab., Univ. California, Berkeley, Calif. 94720, United States

**Corresp. Author/Affil:** : Donner Lab., Lawrence Berkeley Lab., Univ. California, Berkeley, Calif. 94720, United States

Micron ( MICRON ) ( United Kingdom ) December 1, 1978 , 9/4 (175-190)

**CODEN:** MICNB **ISSN:** 0968-4328

**Document Type:** Journal **Record Type:** Abstract

**Language:** English

---

**Dialog eLink:**

**USPTO Full Text Retrieval Options**

13/3/12 (Item 2 from file: 73)

DIALOG(R)File 73: EMBASE

(c) 2009 Elsevier B.V. All rights reserved.

0070101518 **EMBASE No:** 1974101617

**Iron ATP, a by product of acid extraction of whole blood or red blood cells**

Meyers N.L.; Brewer G.J.; Oelshlegel Jr F.J.

Dept. Hum. Genet. Med., Univ. Michigan Med. Sch., Ann Arbor, Mich. 48104, United States

**Corresp. Author/Affil:** : Dept. Hum. Genet. Med., Univ. Michigan Med. Sch., Ann Arbor, Mich. 48104, United States

Biochimica et Biophysica Acta ( BIOCHIM. BIOPHYS. ACTA ) December 1, 1973 , 320/2 (397-405)

**CODEN:** BBACA **ISSN:** 0006-3002

**Document Type:** Journal ; Article **Record Type:** Abstract

**Language:** English

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13/3/13 (Item 1 from file: 135)

DIALOG(R)File 135: NewsRx Weekly Reports

(c) 2009 NewsRx. All rights reserved.

0000571468 (USE FORMAT 7 OR 9 FOR FULLTEXT)

**Studies in the area of microscopy reported from University of Yamanashi**

Life Science Weekly, July 24, 2007, p.2754

DOCUMENT TYPE: Expanded Reporting  
LANGUAGE: English  
RECORD TYPE: FULLTEXT  
WORD COUNT: 427

---

13/3/14 (Item 2 from file: 135)  
DIALOG(R)File 135: NewsRx Weekly Reports  
(c) 2009 NewsRx. All rights reserved.

0000000087 (USE FORMAT 7 OR 9 FOR FULLTEXT)

**Hemolink Phase II Trials to Begin in 1996**  
AIDS Weekly, December 25, 1995, p.11-12

DOCUMENT TYPE: Editor's Choice  
LANGUAGE: English  
RECORD TYPE: FULLTEXT  
WORD COUNT: 763

---

13/3/15 (Item 1 from file: 149)  
DIALOG(R)File 149: TGG Health&Wellness DB(SM)  
(c) 2009 Gale/Cengage. All rights reserved.

01812276 **Supplier Number:** 53480462 (USE FORMAT 7 OR 9 FOR FULL TEXT )  
**Blood relations.(Hemosol Inc's packaging for blood substitute products)**

Canadian Packaging , 51 , 11 , 34(1)  
Nov ,  
1998

**Publication Format:** Magazine/Journal  
ISSN: 0008-4654  
**Language:** English  
**Record Type:** Fulltext **Target Audience:** Trade  
**Word Count:** 1076 **Line Count:** 00094

**Special Features:** illustration; 1  
**Company Names:** Hemosol Inc.--Products  
**Descriptors:** Blood substitutes--Packaging; Blood products--Packaging; Packaging industry --Products  
**Geographic Codes/Names:** 1USA United States  
**SIC Codes:** 2836 Biological products exc. diagnostic; 2670 Misc. Converted Paper

Products

**Event Codes/Names:** 460 Use of materials & supplies

**Product/Industry Names:** 2833440 (Synthetic Blood); 2649910 (Sterilized Medical Packaging)

**File Segment:** TI File 148

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13/3/16 (Item 2 from file: 149)

DIALOG(R)File 149: TGG Health&Wellness DB(SM)

(c) 2009 Gale/Cengage. All rights reserved.

01641618 **Supplier Number:** 18748015 (USE FORMAT 7 OR 9 FOR FULL TEXT )

**Blood substitute offers advantages. (experimental Hemolink, a red blood cell substitute from Hemosol Inc, does not possess the disadvantages of donated blood)(Brief Article)**

USA Today (Magazine) , v124 , n2609 , p13(1)

Feb ,

1996

**Document Type:** Brief Article **Publication Format:** Magazine/Journal

ISSN: 0161-7389

**Language:** English

**Record Type:** Fulltext **Target Audience:** Consumer

**Word Count:** 459 **Line Count:** 00041

**Special Features:** illustration; photograph

**Company Names:** Hemosol Inc.--Product development

**Descriptors:** Blood substitutes--Innovations

**File Segment:** MI File 47

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13/3/17 (Item 3 from file: 149)

DIALOG(R)File 149: TGG Health&Wellness DB(SM)

(c) 2009 Gale/Cengage. All rights reserved.

01193508 **Supplier Number:** 08093457 (USE FORMAT 7 OR 9 FOR FULL TEXT )

**Synthesis of functional human hemoglobin in transgenic mice.**

Behringer, Richard R.; Ryan, Thomas M.; Reilly, Michael P.; Asakura, Toshio ; Palmiter, Richard D.; Brinster, Ralph L.; Townes, Tim M.

Science , v245 , n4921 , p971(3)

Sept 1 ,

1989

**Publication Format:** Magazine/Journal

ISSN: 0036-8075

**Language:** English

**Record Type:** Fulltext **Target Audience:** Academic

**Word Count:** 2144 **Line Count:** 00213

**Special Features:** illustration; chart; graph

**Descriptors:** Mice as laboratory animals--Research; Gene expression--Research; Hemoglobinopathy--Models; Genetic transformation--Research; Hemoglobin-- Research

**File Segment:** MI File 47

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**Dialog eLink:**

USPTO Full Text Retrieval Options

13/3/18 (Item 1 from file: 162)

DIALOG(R)File 162: Global Health

(c) 2009 CAB International. All rights reserved.

0004754137 **CAB Accession Number:** 20002007317

**KEMRI Hep-cell II hepatitis B surface antigen screening kit.**

Okoth, F. A.; Kaiguri, P. M.; Mathenge, E.; Tuei, J.; Muchiri, S.; Owino, N.; Kamau, G.; Kulundu, J.; Njuguna, A.; Tukei, P. M.; Yano, M.; Naruse, T.

Virus Research Centre, Kenya Medical Research Institute, P.O. Box 54628, Nairobi, Kenya.

East African Medical Journal vol. 76 ( 9 ): p.530-532

**Publication Year:** 1999

**ISSN:** 0012-835X

**Language:** English **Record Type:** Abstract

**Document Type:** Journal article

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13/3/19 (Item 1 from file: 444)

DIALOG(R)File 444: New England Journal of Med.

(c) 2009 Mass. Med. Soc. All rights reserved.

00103092

Copyright 1987 by the Massachusetts Medical Society

**Elevated Fetal Hemoglobin Levels in Sudden Infant Death Syndrome (Original Article)**

Giulian, Gary G., B.A.; Gilbert, Enid F.; Moss, Richard L., Ph.D.

The New England Journal of Medicine

April 30 , 1987 ; 316 (18),pp 1122-1126



**Line Count:** 00337

**Word Count:** 04654

? t s13/full/all

**Dialog eLink:**

USPTO Full Text Retrieval Options

13/9/1 (Item 1 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

17948132 **PMID:** 17393480

**Raman microscopy of freeze-dried mouse eyeball-slice in conjunction with the "in vivo cryotechnique".**

Terada Nobuo; Ohno Nobuhiko; Saitoh Sei; Fujii Yasuhisa; Ohguro Hiroshi; Ohno Shinichi

Department of Anatomy, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Chuo-city, Yamanashi 409-3898, Japan.

nobuot@yamanashi.ac.jp

Microscopy research and technique ( United States ) Jul 2007 , 70 (7) p634-9 , **ISSN:** 1059-910X--Print **Journal Code:** 9203012

Publishing Model Print

**Document type:** Journal Article

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

**Subfile:** INDEX MEDICUS

The wavelength of Raman-scattered light depends on the molecular composition of the substance. This is the first attempt to acquire Raman spectra of a mouse eyeball removed from a living mouse, in which the eyeball was preserved using the "in vivo cryotechnique" followed by freeze-drying. Eyeballs were cryofixed using a rapid freezing cryotechnique, and then sliced in the cryostat machine. The slices were sandwiched between glass slides, freeze-dried, and analyzed with confocal Raman microscopy. Important areas including various eyeball tissue layers were selected using bright-field microscopy, and then the Raman spectra were obtained at 240 locations. Four typical patterns of Raman spectra were electronically mapped on the specimen images obtained by the bright-field microscopy. Tissue organization was confirmed by embedding the same eyeball slice used for Raman spectra into epoxy resin and the thick sections were prepared with the inverted capsule method. Each Raman spectral pattern represents a different histological layer in the eyeball which was mapped by comparing the images of toluidine blue staining and Raman mapping with different colors. In the choroid and pigment cell layer, the Raman spectrum had two peaks, corresponding to melanin. Some of the peaks of the Raman spectra obtained from the blood vessels in sclera and the photoreceptor layer were similar to those obtained from the purified hemoglobin and rhodopsin proteins, respectively. Our experimental protocol can distinguish different tissue components with Raman microscopy; therefore, this method can be very useful for

examining the distribution of a biological structures and/or chemical components in rapidly frozen freeze-dried tissue.

**Descriptors:** \*Cryopreservation--methods--MT; \*Eye--anatomy and histology--AH; \*Eye --chemistry--CH; \*Microscopy, Confocal--methods--MT; \*Spectrum Analysis, Raman--methods--MT ; Animals; Cryoultramicrotomy--methods--MT; Freeze Drying; Hemoglobins --analysis--AN; Mice; Preservation, Biological; Rhodopsin--analysis--AN; Specimen Handling

**CAS Registry No.:** 0 (Hemoglobins); 9009-81-8 (Rhodopsin)

**Record Date Created:** 20070625

**Record Date Completed:** 20070731

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**Dialog eLink:**

**ISPTO Full Text Retrieval Options**

13/9/2 (Item 2 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

(c) format only 2009 Dialog. All rights reserved.

12318632 **PMID:** 9054405

**The globin-based free radical of ferryl hemoglobin is detected in normal human blood.**

Svistunenko D A; Patel R P; Voloshchenko S V; Wilson M T

Department of Biological and Chemical Sciences, Central Campus, University of Essex, Colchester, Essex CO4 3SQ, United Kingdom.

Journal of biological chemistry ( UNITED STATES ) Mar 14 1997 , 272 (11) p7114-21 , **ISSN:** 0021-9258--Print **Journal Code:** 2985121R

Publishing Model Print

**Document type:** Journal Article; Research Support, Non-U.S. Gov't

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

**Subfile:** INDEX MEDICUS

Normal human venous blood was studied by electron paramagnetic resonance (EPR) spectroscopy at -196 degrees C. The EPR signal of free radicals in frozen blood is shown to have the same radiospectroscopic parameters and properties as the signal of the globin based free radical, .Hb(Fe(IV)=O), formed in the reaction of purified methemoglobin (metHb) with H<sub>2</sub>O<sub>2</sub> and therefore has been assigned as such. The globin-based radicals and metHb exhibited significant variation (fluctuations) in different frozen samples taken from the same liquid blood sample. In any given sample a high concentration of free radicals was associated with a low concentration of metHb and vice versa, i.e. the fluctuations were always of opposite sense. No such fluctuations were observed in the concentration of two other paramagnetic components of blood, transferrin and ceruloplasmin. The time course of free radical formation and decay upon the addition of H<sub>2</sub>O<sub>2</sub> to purified metHb was studied at three different molar ratios H<sub>2</sub>O<sub>2</sub>/metHb. This kinetic study together with the results of an annealing experiment allow us to propose a

mechanism for the formation and decay of the globin-based radical in blood. Within this mechanism, the source of H<sub>2</sub>O<sub>2</sub> in blood is considered to be dismutation of O<sub>2</sub> radicals produced via autoxidation of Hb. We postulate that the dismutation is intensified on the phase separation surfaces during cooling and freezing of a blood sample. The fluctuations are explained within this hypothesis.

**Descriptors:** \*Globins--chemistry--CH; \*Hemoglobins--chemistry--CH ; Electron Spin Resonance Spectroscopy; Free Radicals--blood--BL; Humans; Iron--chemistry--CH

**CAS Registry No.:** 0 (Free Radicals); 0 (Hemoglobins); 7439-89-6 (Iron); 9004-22-2 (Globins)

**Record Date Created:** 19970417

**Record Date Completed:** 19970417

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**Dialog eLink:**

**ISPTO Full Text Retrieval Options**

13/9/3 (Item 3 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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11308907 **PMID:** 7994369

**Stabilized hemoglobin vesicles.**

Tsuchida E

Department of Polymer Chemistry, Waseda University, Tokyo, Japan.

Artificial cells, blood substitutes, and immobilization biotechnology ( UNITED STATES ) 1994 , 22 (3) p467-77 , **ISSN:** 1073-1199--Print **Journal Code:** 9431307

Publishing Model Print

**Document type:** In Vitro; Journal Article

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

**Subfile:** INDEX MEDICUS

The Hb-vesicles which encapsulate the purified and concentrated Hb more than 40 g/dl with a uni- or bi-lamellar membrane are prepared by extruding the dispersion of mixed lipids through membrane filters (final pore size: 0.2 micron phi). They transport large amount of oxygen with satisfying rheological properties such as oncotic pressure and solution viscosity. Oxygen affinity of the Hb-vesicles is adjusted so as to exceed the ability of oxygen transport of human blood by coencapsulating allosteric effectors in the Hb-vesicles. The solution is sterilizable because of the diameter of Hb vesicles less than 0.2 micron phi. The Hb-vesicles are stabilized by using polyphospholipid or glycolipid as membrane components. No change in oxygen affinity and particle size was confirmed during long time storage at 4 degrees C. The stabilized Hb-vesicles can also be stored as frozen or dried state. The dried Hb-vesicles are regenerated by simply adding pure water. Simple in vitro test indicates that Hb-vesicles have the reduced inhibitory action of Hb to the EDRF-mediated vasorelaxation.

**Tags:** Female; Male

**Descriptors:** \*Blood Substitutes--isolation and purification--IP; \*Hemoglobins--isolation and purification--IP ; Acetylcholine--antagonists and inhibitors--AI; Acetylcholine--pharmacology --PD; Animals; Blood Substitutes--chemistry--CH; Blood Substitutes --pharmacology--PD; Drug Stability; Drug Storage; Hemoglobins--chemistry --CH; Hemoglobins--pharmacology--PD; Humans; Liposomes; Nitric Oxide --antagonists and inhibitors--AI; Nitric Oxide--pharmacology--PD; Particle Size; Rabbits; Solutions; Vasodilation--drug effects--DE; Vehicles

**CAS Registry No.:** 0 (Blood Substitutes); 0 (Hemoglobins); 0 (Liposomes); 0 (Solutions); 0 (Vehicles); 0 (hemoglobin, stroma free); 10102-43-9 (Nitric Oxide); 51-84-3 (Acetylcholine)

**Record Date Created:** 19950117

**Record Date Completed:** 19950117

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**Dialog eLink:**

USPTO Full Text Retrieval Options

13/9/4 (Item 4 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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10533593 **PMID:** 1457926

**Characteristics of artificial red cells. Hemoglobin encapsulated in poly-lipid vesicles.**

Satoh T; Kobayashi K; Sekiguchi S; Tsuchida E

Tsukuba Research Laboratories, NOF Corporation, Japan.

ASAIO journal (American Society for Artificial Internal Organs - 1992) ( UNITED STATES ) Jul-Sep 1992 , 38 (3) pM580-4 , **ISSN:** 1058-2916--Print **Journal Code:** 9204109

Publishing Model Print

**Document type:** In Vitro; Journal Article

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

**Subfile:** INDEX MEDICUS; Toxbib

Artificial red cells (ARC) were prepared by encapsulation of purified human Hb with polymerizable phospholipid, 1,2-bis (2,4-octadecadienoyl)-sn-glycero-3-phosphocholine (DODPC). The polymerized lipid bilayer of the ARC produced great physical stability that could not be achieved using a non-polymerizable lipid for encapsulation. ARC showed no change in particle size or distribution or leakage of Hb after repeated freeze thawing (stability test). ARC have also been studied with regard to biocompatibility. The authors' results showed low acute toxicity (> 8000 mg/kg) and adequate blood compatibility. The result of transfusion tests in dogs showed that ARC had sufficient oxygen transporting capabilities.

**Tags:** Male

**Descriptors:** \*Blood Substitutes; \*Hemoglobins ; Animals; Biocompatible Materials; Blood Substitutes--isolation and purification--IP; Blood Substitutes--toxicity--TO; Dogs;

Drug Stability; Erythrocyte Aggregation; Evaluation Studies as Topic; Exchange Transfusion, Whole Blood; Freezing; Humans; Liposomes; Materials Testing; Oxygen--blood --BL; Phosphatidylcholines; Rats; Rats, Sprague-Dawley

**CAS Registry No.:** 0 (Biocompatible Materials); 0 (Blood Substitutes); 0 (Hemoglobins); 0 (Liposomes); 0 (Phosphatidylcholines); 7782-44-7 (Oxygen)

**Record Date Created:** 19930111

**Record Date Completed:** 19930111

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**Dialog eLink:** [JSP19 Full Text Retrieval Options](#)

13/9/5 (Item 5 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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10049338 **PMID:** 1918801

**Preparation of unaltered hemoglobin from human placentas for possible use in blood substitutes.**

Fasan G; Grandgeorge M; Vigneron C; Dellacherie E

CNRS URA 494, ENSIC, Nancy, France.

Journal of biochemical and biophysical methods ( NETHERLANDS ) Jul-Aug 1991 , 23 (1) p53-66 , **ISSN:** 0165-022X--Print **Journal Code:** 7907378

Publishing Model Print

**Document type:** Journal Article

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

**Subfile:** INDEX MEDICUS

Hemoglobin extracted from human placentas could be used as the basis of blood substitutes provided it could be prepared on a large scale with appropriate oxygen-binding properties. Unfortunately, the industrial conditions under which it is extracted, produce hemoglobin with high oxygen affinity and which is no longer influenced by the classical effectors. These characteristics were shown to be caused by a degradation of the alpha-chain brought about by an arginine carboxypeptidase present in the placental tissues and leading to the disappearance of the C-terminal arginine residue. This carboxypeptidase which is released from the tissues during the process of crushing the frozen placentas, degrades the protein during the chromatographic purification procedure. The addition of an inhibitor of this carboxypeptidase (for example, arginine) as soon as the placentas are thawed and during the chromatographic process, makes it possible to obtain placental hemoglobin with oxygen-binding properties quite similar to those of HbA prepared from peripheral venous blood.

**Descriptors:** \*Blood Substitutes--chemistry--CH; \*Hemoglobins--isolation and purification --IP; \*Placenta--chemistry--CH ; Adult; Arginine--pharmacology--PD; Carboxypeptidase B; Carboxypeptidases --pharmacology--PD; Hemoglobin A--drug effects--DE; Hemoglobins--chemistry --CH; Humans; Oxygen--blood--BL; Plasma--

physiology--PH; Protein Binding

**CAS Registry No.:** 0 (Blood Substitutes); 0 (Hemoglobins); 74-79-3 (Arginine); 7782-44-7 (Oxygen); 9034-51-9 (Hemoglobin A)

**Enzyme No.:** EC 3.4.- (Carboxypeptidases); EC 3.4.17.2 (Carboxypeptidase B)

**Record Date Created:** 19911028

**Record Date Completed:** 19911028

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**Dialog eLink:**

**USPTO Full Text Retrieval Options**

13/9/6 (Item 6 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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09774516 **PMID:** 2289306

**Polymerase chain reaction: amplification of DNA from fixed tissue.**

Crisan D; Cadoff E M; Mattson J C; Hartle K A

Department of Pathology, University of Pittsburgh, PA 15213-2582.

Clinical biochemistry ( CANADA ) Dec 1990 , 23 (6) p489-95 , **ISSN:** 0009-9120--

Print **Journal Code:** 0133660

Publishing Model Print

**Document type:** Journal Article; Research Support, Non-U.S. Gov't

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

**Subfile:** INDEX MEDICUS

The polymerase chain reaction (PCR) allows the analysis of DNA from biologic samples containing only nanogram quantities of DNA. We used DNA purified from fresh or frozen peripheral blood (PB) leukocytes and formalin, or B-5 fixed bone marrow aspirate clots (BM). A sequence of the beta-globin gene was amplified via the PCR then hybridized with allele specific oligonucleotide probes for hemoglobin A, S, and C. All DNA preparations, including formalin and B-5 fixed BMs, were successfully amplified; the hybridization of the amplified products resulted in patterns consistent with the hemoglobin phenotype for all patients. PCR can be used on DNA from many sources; retrospective studies using paraffin embedded fixed tissue are possible because extremely small amounts of DNA present in fixed tissue can be successfully amplified.

**Tags:** Female; Male

**Descriptors:** \*Polymerase Chain Reaction--methods--MT ; Adult; Aged; Aged, 80 and over; Base Sequence; DNA--genetics--GE; DNA Probes; DNA, Single-Stranded--genetics--GE; Fixatives; Formaldehyde; Humans ; Middle Aged; Molecular Sequence Data; Nucleic Acid Hybridization; Specimen Handling--methods--MT

**CAS Registry No.:** 0 (DNA Probes); 0 (DNA, Single-Stranded); 0 (Fixatives); 50-00-0 (Formaldehyde); 9007-49-2 (DNA)

**Record Date Created:** 19910329

**Record Date Completed:** 19910329

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**Dialog eLink:**

**ISPTO Full Text Retrieval Options**

13/9/7 (Item 7 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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05307246 **PMID:** 951729

**Preparation of antihemophilic factor from indated plasma.**

Wickerhauser M

Transfusion ( UNITED STATES ) Jul-Aug 1976 , 16 (4) p345-50 , **ISSN:** 0041-1132-  
-Print **Journal Code:** 0417360

Publishing Model Print

**Document type:** Journal Article; Research Support, U.S. Gov't, Non-P.H.S.

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

**Subfile:** INDEX MEDICUS

Four large-scale batches of Antihemophilic Factor (AHF, factor VIII) were prepared from plasma derived from 4 to 6-day-old blood applying a method developed for preparation of AHF from fresh frozen plasma. The AHF product was 6 to 9-fold concentrated over plasma with 7 to 10-fold purification and a recovery of 100 to 140 factor VIII units per liter of starting plasma. In terms of purity and yield, this is about half that of AHF obtained from fresh frozen plasma. The AHF concentrate was free of detectable thrombin and plasmin and the solubility of the dry product was comparable to that of the product derived from fresh plasma but the hemoglobin content was slightly increased. After further fractionation with polyethylene glycol (PEG 4000), a highly soluble AHF product 100-fold purified, and 30-fold concentrated, was obtained with 60% factor VIII recovery, which corresponds to a final yield of 60 to 85 factor VIII units per liter of starting plasma.

**Descriptors:** \*Factor VIII--isolation and purification--IP; \*Plasma ; Factor VIII--analysis--AN; Fractional Precipitation; Hemoglobins--analysis --AN; Humans;

Polyethylene Glycols; Time Factors

**CAS Registry No.:** 0 (Hemoglobins); 0 (Polyethylene Glycols); 9001-27-8 (Factor VIII)

**Record Date Created:** 19761002

**Record Date Completed:** 19761002

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**Dialog eLink:**

**ISPTO Full Text Retrieval Options**

13/9/8 (Item 8 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

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04293564 **PMID:** 5005879

**Recent advances in the field of red cell structure.**

Baker R F

Pathobiology annual ( UNITED STATES ) 1971 , 1 p95-137 , **ISSN:** 0362-3025--

Print **Journal Code:** 1305471

Publishing Model Print

**Document type:** Journal Article; Review

**Languages:** ENGLISH

**Main Citation Owner:** NLM

**Record type:** MEDLINE; Completed

**Subfile:** INDEX MEDICUS

( 130 Refs.)

**Descriptors:** \*Erythrocytes--cytology--CY ; Adenosine Triphosphate--isolation and purification--IP; Amino Acids--blood --BL; Anemia, Sickle Cell--blood--BL; Anemia, Sickle Cell--pathology--PA; Animals; Blood; Blood Group Antigens; Cell Membrane--analysis--AN; Cytological Techniques; Erythrocytes--analysis--AN; Erythrocytes --immunology--IM; Freeze Etching; Glutaral; Guinea Pigs; Hemoglobin, Sickle --analysis--AN; Humans; Lipids--blood--BL; Magnetic Resonance Spectroscopy; Microscopy, Electron; Microscopy, Electron, Scanning; Microtubules; Proteins--analysis--AN

**CAS Registry No.:** 0 (Amino Acids); 0 (Blood Group Antigens); 0 (Hemoglobin, Sickle); 0 (Lipids); 0 (Proteins); 111-30-8 (Glutaral); 56-65-5 (Adenosine Triphosphate)

**Record Date Created:** 19740328

**Record Date Completed:** 19740328

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**Dialog eLink:**

**USP10 Full Text Retrieval Options**

13/9/9 (Item 1 from file: 50)

DIALOG(R)File 50: CAB Abstracts

(c) 2009 CAB International. All rights reserved.

0008083726 **CAB Accession Number:** 20013088268

**Gemobin - a new-generation natural biologically active food supplement.**

Chernyaev, S. I.; Lyublinskii, S. L.; Lyublinskaya, I. N.; Markov, M. V.

Dep. Sel'skogo Khozyaistva I Prodovol'stviya, Kaluga obl., Russia.

Pishchevaya Promyshlennost' ( 6 ): p.50-52

**Publication Year:** 2000

**ISSN:** 0235-2486

**Publisher:** OOO "Pishchepromizdat" Moscow , Russia

**Language:** Russian **Record Type:** Abstract

**Document Type:** Journal article

Gemobin [Haemobin] is a purified native freeze-dried haemoglobin from the blood of cattle, containing 0.2-0.3% iron (bivalent form). This preparation is produced on an industrial scale in Russia by the Mobitek company, in the form of tablets, sugared



'plums', and Supergematogen sticks with a coconut filling. It is designed to remedy iron deficiency, and a comparison is made between Russia and Western countries in approaches to treating iron deficiency.

**Descriptors:** deficiency; food supplements; haemoglobin; iron; mineral supplements; supplements; trace elements

**Identifiers:** hemoglobin; microelements

**CAS Registry Numbers:** 7439-89-6

**Organism Descriptors:** man

**Geographic Names:** Russia

**Broader Terms:** Homo; Hominidae; Primates; mammals; vertebrates; Chordata; animals; eukaryotes; Asia; Central Europe; Europe; Developed Countries

**CABICodes:** Nutrition related Disorders and Therapeutic Nutrition (VV130); Meat Produce (QQ030)

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13/9/10 (Item 1 from file: 71)

DIALOG(R)File 71: ELSEVIER BIOBASE

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0007196715      **Supplier Number:** 2007196786

**Raman microscopy of freeze-derived mouse eyeball-slice in conjunction with "in vivo cryotechnique"**

Terada N.; Ohno N.; Saitoh S.; Fujii Y.; Ohguro H.; Ohno S.

**Author Email:** nobuot@yamanashi.ac.jp

**Corresp. Author/Affil:** Terada N., Department of Anatomy, Interdisciplinary Graduate School of, Medicine and Engineering, University of Yamanashi, 1110 Shimokato, Chuo-city, Yamanashi 409-3898 , Japan

**Corresp. Author Email:** nobuot@yamanashi.ac.jp

Journal : Microscopy Research and Technique (Microsc. Res. Tech. ) , v70, n7, (634-639) , 2007 , United States

**Publication Date:** July 1, 2007 (20070701 )

**Coden:** MRTEE

**ISSN:** 1059-910X **eISSN:** 1097-0029

**DOI:** <http://dx.doi.org/10.1002/jemt.20449>

**Record Type:** Abstract; New

**Document Type:** Article

**Languages:** English      **Summary Languages:** English

**No. of References:** 20

The wavelength of Raman-scattered light depends on the molecular composition of the substance. This is the first attempt to acquire Raman spectra of a mouse eyeball removed from a living mouse, in which the eyeball was preserved using the "in vivo cryotechnique" followed by freeze-drying. Eyeballs were cryofixed using a rapid freezing cryotechnique, and then sliced in the cryostat machine. The slices were sandwiched between glass slides, freeze-dried, and analyzed with confocal Raman microscopy.

Important areas including various eyeball tissue layers were selected using bright-field microscopy, and then the Raman spectra were obtained at 240 locations. Four typical patterns of Raman spectra were electronically mapped on the specimen images obtained by the bright-field microscopy. Tissue organization was confirmed by embedding the same eyeball slice used for Raman spectra into epoxy resin and the thick sections were prepared with the inverted capsule method. Each Raman spectral pattern represents a different histological layer in the eyeball which was mapped by comparing the images of toluidine blue staining and Raman mapping with different colors. In the choroid and pigment cell layer, the Raman spectrum had two peaks, corresponding to melanin. Some of the peaks of the Raman spectra obtained from the blood vessels in sclera and the photoreceptor layer were similar to those obtained from the purified hemoglobin and rhodopsin proteins, respectively. Our experimental protocol can distinguish different tissue components with Raman microscopy; therefore, this method can be very useful for examining the distribution of a biological structures and/or chemical components in rapidly frozen freeze-dried tissue. (c) 2007 Wiley-Liss, Inc.

**Descriptors:**

Freeze-drying; In vivo cryotechnique; Mapping; Raman microscopy; Raman spectrum

**Classification Code and Description:**

89 (CELL AND DEVELOPMENTAL BIOLOGY)

89.13 (METHODOLOGY)

89.13.1 (Techniques)

89.13.1.3 (Microscopy)

**Record History:** New; Created: July 20, 2007 (20070720 ) ; Delivered: June 22, 2008 (20080622 )

**Dialog Update Date:** 20081211; 08:07:19 EST

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**Dialog eLink:**

**ISPTO Full Text Retrieval Options**

13/9/11 (Item 1 from file: 73)

DIALOG(R)File 73: EMBASE

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0071381872    **EMBASE No:** 1979114101

**Analysis of iron content in individual human red blood cells by electron microprobe and scanning electron microscope**

Davis D.

Donner Lab., Lawrence Berkeley Lab., Univ. California, Berkeley, Calif. 94720, United States

**Corresp. Author/Affil:** : Donner Lab., Lawrence Berkeley Lab., Univ. California, Berkeley, Calif. 94720, United States

Micron ( MICRON ) ( United Kingdom ) December 1, 1978 , 9/4 (175-190)

**CODEN:** MICNB **ISSN:** 0968-4328

**Document Type:** Journal **Record Type:** Abstract

**Language:** English

The iron content of single human red blood cells has been assessed using electron microprobe analysis and scanning electron microscope. Cells for microanalysis consist of a fixed-washed and freeze-dried preparation. This preparative procedure improves stability and spatial resolution of the analytic method. The reference standard employs compressed pellets of purified iron-containing human hemoglobin and human albumin, respectively. The cell preparation and reference standard remain stable for long periods of time. Differences in Fe content and its distribution among individual red cells from both normal subjects and sickle cell anaemia patients have been measured by the quantitative and semiquantitative techniques (wavelength and energy dispersive X-ray spectrometry). There are several points which can be made from this study. One concerns the estimate of iron on a cell by cell basis, the average variation can be made from this study. One concerns the estimate of iron on a cell by cell basis, the average variation among cells being slightly over 13%, ranging from 6% to 19.4% by individuals (samples) or from 11% to 14% by ethnic groups. These differences are thus closely comparable across ethnic grouping with a possibility of high level in Asians and lower level in sickle cell anaemia patients.

**Drug Descriptors:**

\* iron

**Medical Descriptors:**

\* erythrocyte

blood and hemopoietic system; cytology; diagnosis; methodology

**CAS Registry Number:** 14093-02-8, 53858-86-9, 7439-89-6 (iron)

**SECTION HEADINGS:**

Anatomy, Anthropology, Embryology and Histology

Hematology

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**Dialog eLink:**

USPTO Full Text Retrieval Options

13/9/12 (Item 2 from file: 73)

DIALOG(R)File 73: EMBASE

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0070101518 **EMBASE No:** 1974101617

**Iron ATP, a by product of acid extraction of whole blood or red blood cells**

Meyers N.L.; Brewer G.J.; Oelshlegel Jr F.J.

Dept. Hum. Genet. Med., Univ. Michigan Med. Sch., Ann Arbor, Mich. 48104, United States

**Corresp. Author/Affil:** : Dept. Hum. Genet. Med., Univ. Michigan Med. Sch., Ann

Arbor, Mich. 48104, United States

Biochimica et Biophysica Acta ( BIOCHIM. BIOPHYS. ACTA ) December 1, 1973 ,  
320/2 (397-405)

**CODEN:** BBACA **ISSN:** 0006-3002

**Document Type:** Journal ; Article **Record Type:** Abstract

**Language:** English

Trichloroacetic acid extracts of red cells often produce an iron ATP complex after ion exchange chromatography of the extract amounting to about 1/3 of the total ATP. In the present work the presence of 14-50% of iron ATP in such extracts from human and Rhesus monkey blood has been shown. Experiments designed to clarify the possible role and origin of iron ATP revealed that non acid treatment of human whole blood or red cells, as in the freeze thaw process, followed by separation on a Sephadex column did not produce an iron ATP fraction. In addition, purified hemoglobin and ATP were combined and incubated at pH 7.4. After Sephadex chromatography, there was no evidence of an iron ATP fraction. However, similar combinations of incubated hemoglobin and ATP treated with trichloroacetic acid and separated by ion exchange chromatography did produce an iron ATP fraction similar to that obtained from acid extracted blood. It appears that iron ATP in quantities found in acid extracted blood is the result of iron release from hemoglobin and the subsequent complexing of such iron with available ATP.

**Drug Descriptors:**

\* adenosine triphosphate  
unclassified drug

**Medical Descriptors:**

\* erythrocyte  
article; in vitro study; normal human; theoretical study

**Drug Terms (Uncontrolled):** caffeic acid rhamnoglucoside

**CAS Registry Number:** 15237-44-2, 56-65-5, 987-65-5 (adenosine triphosphate)

**SECTION HEADINGS:**

Clinical and Experimental Biochemistry  
Hematology

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13/9/13 (Item 1 from file: 135)  
DIALOG(R)File 135: NewsRx Weekly Reports  
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0000571468 (THIS IS THE FULLTEXT)

**Studies in the area of microscopy reported from University of Yamanashi**  
Life Science Weekly, July 24, 2007, p.2754

DOCUMENT TYPE: Expanded Reporting

LANGUAGE: English

RECORD TYPE: FULLTEXT

AUDIENCE: Professional

WORD COUNT: 427

TEXT:

New research, "Raman microscopy of freeze-dried mouse eyeball-slice in conjunction with the "in vivo cryotechnique", is the subject of a report. "The wavelength of Raman-scattered light depends on the molecular composition of the substance. This is the first attempt to acquire Raman spectra of a mouse eyeball removed from a living mouse, in which the eyeball was preserved using the "in vivo cryotechnique" followed by freeze-drying," scientists writing in the journal *Microscopy Research and Technique* report. "Eyeballs were cryofixed using a rapid freezing cryotechnique, and then sliced in the cryostat machine. The slices were sandwiched between glass slides, freeze-dried, and analyzed with confocal Raman microscopy. Important areas including various eyeball tissue layers were selected using bright-field microscopy, and then the Raman spectra were obtained at 240 locations. Four typical patterns of Raman spectra were electronically mapped on the specimen images obtained by the bright-field microscopy. Tissue organization was confirmed by embedding the same eyeball slice used for Raman spectra into epoxy resin and the thick sections were prepared with the inverted capsule method. Each Raman spectral pattern represents a different histological layer in the eyeball which was mapped by comparing the images of toluidine blue staining and Raman mapping with different colors. In the choroid and pigment cell layer, the Raman spectrum had two peaks, corresponding to melanin. Some of the peaks of the Raman spectra obtained from the blood vessels in sclera and the photoreceptor layer were similar to those obtained from the purified hemoglobin and rhodopsin proteins, respectively," wrote N. Terada and colleagues, University of Yamanashi. The researchers concluded: "Our experimental protocol can distinguish different tissue components with Raman microscopy; therefore, this method can be very useful for examining the distribution of a biological structures and/or chemical components in rapidly frozen freeze-dried tissue." Terada and colleagues published their study in

*Microscopy Research and Technique* (Raman microscopy of freeze-dried mouse eyeball-slice in conjunction with the "in vivo cryotechnique" *Microscopy Research and Technique* , 2007;70(7):634-9). Additional information can be obtained by contacting N. Terada, University of Yamanashi, Dept. of Anatomy, Interdisciplinary Graduate School of Medicine and Engineering, Chuo-city, Yamanashi 409-3898, Japan. The publisher of the journal *Microscopy Research and Technique* can be contacted at: Wiley-Liss, Division John Wiley & Sons Inc., 111 River St., Hoboken, NJ 07030, USA. Keywords: Japan, Yamanashi, Microscopy. This article was prepared by Life Science Weekly editors from staff and other reports. Copyright 2007, Life Science Weekly via NewsRx.com & NewsRx.net.

DESCRIPTORS: All News; Professional News; All News; Professional News

SUBJECT HEADING: Microscopy

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13/9/14 (Item 2 from file: 135)  
DIALOG(R)File 135: NewsRx Weekly Reports  
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0000000087 (THIS IS THE FULLTEXT)

**Hemolink Phase II Trials to Begin in 1996**

AIDS Weekly, December 25, 1995, p.11-12

DOCUMENT TYPE: Editor's Choice

LANGUAGE: English

RECORD TYPE: FULLTEXT

AUDIENCE: Professional

WORD COUNT: 763

**TEXT:**

A red blood cell substitute will go into Phase II clinical trials early in 1996 and, if all goes well, could be available on the market by 1999.

The announcement was made at the 1995 International Chemical Congress of Pacific Basin Societies, held in Honolulu, Hawaii, December 17-22, 1995.

The blood substitute, Hemolink, manufactured by Hemosol, is made of chemically modified hemoglobin, says Dr. Gord Adamson, a company scientist. Hemolink is derived from screened and tested blood that is outdated because it has been stored for more than six weeks.

Hemosol takes the expired blood, separates out the red blood cells and extracts the hemoglobin. That's more complicated than it sounds. "A red cell is not just a package of clean hemoglobin," Adamson says. "It contains about 90 different proteins." The company heat-treats the hemoglobin to destroy any contaminating viruses that may have eluded the screening process conducted by collection agencies. Other remaining proteins are then removed by a novel displacement chromatographic process.

The process strips away blood-group antigens and other proteins, so Hemolink can be used by all patients regardless of blood type. And the purification steps make the likelihood of transmission of diseases such as HIV and hepatitis "virtually" nil, according to Adamson.

"The reason we say 'virtually,'" he notes, "is because scientifically it is impossible to prove total absence of a virus," but he is very confident that Hemolink would pose no threat to users in terms of blood-borne diseases. In addition, the blood from which Hemolink is derived is already approved for use; the company does not accept contaminated units.

After purification, the free hemoglobin is cross-linked with oxidized raffinose, a sugar molecule. This "improves the ability of the free hemoglobin to deliver oxygen to tissue, stabilizes each hemoglobin molecule and links together several such molecules so that

they are large enough to circulate for extended periods," Adamson says.

Human trials with Hemolink show the blood substitute circulates for a couple of days in the blood stream - compared with a month or more for transfused red cells - and is then excreted, says Adamson. But animal trials show this is long enough to counteract oxygen shortages during acute blood loss, say, in an accident or an operation. In fact, these trials showed that animals treated with Hemolink did just as well as those treated with transfusions of the animals' own blood.

Hemosol is currently working with two versions of Hemolink, one a fluid stored in a refrigerator and one frozen. Either formulation would be suitable for surgical applications. A long-term goal is to develop a freeze-dried formulation. It would be light enough to ship to remote depots - for use in disasters or military conflicts, for example - and it could be reconstituted with sterile water on-site.

Adamson believes the cost for Hemolink would be competitive, noting that there are significant administrative costs associated with the existing blood collection and distribution system. These include the storage, transport, disposal and other labor and record-keeping activities that a successful blood substitute would significantly reduce. Also, since no cross-matching would be required, these costs would be saved.

Hemolink also would avoid some of the costly problems associated with blood transfusions - such as transmission of disease (ranging from HIV or hepatitis to a bacterial infection), or mismatched blood (where the patient might have a reaction to antigens in the donor's blood that could be mild, such as a fever, or severe, resulting in death), or the delays in surgery brought about by blood shortages.

Hemosol will not rely just on Hemolink to launch itself in this market. The company is collaborating with Ronald Kluger, a chemistry professor with the University of Toronto, Ontario, Canada, to further extend cross-linking technologies for second-generation products.

Adamson says the work also is aimed at chemically modifying hemoglobin so it can serve as a carrier for drug molecules. Tissues that can accumulate and metabolize protein-drug conjugates are potential targets. An example is a solid tumor. Adamson says this would reduce many of the side-effects of anti-tumor agents.

A large-scale conversion from red cells to blood substitutes is unrealistic, particularly in the short term, Adamson says. But assuming they win approval, blood substitutes could ultimately bring in big money. Industry estimates of the potential market for blood substitutes (and newer applications where red cells can't be used) by the year 2002 are around 1.5 million units (worth US\$500 million) in North America, and over three million units worldwide, Hemosol says.

DESCRIPTORS: news

SUBJECT HEADING: Industry News (Blood Substitutes)

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13/9/15 (Item 1 from file: 149)

DIALOG(R)File 149: TGG Health&Wellness DB(SM)

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01812276    **Supplier Number:** 53480462 (THIS IS THE FULL TEXT )  
**Blood relations.(Hemosol Inc's packaging for blood substitute products)**

Canadian Packaging , 51 , 11 , 34(1)

Nov ,  
1998

**Publication Format:** Magazine/Journal

ISSN: 0008-4654

**Language:** English

**Record Type:** Fulltext   **Target Audience:** Trade

**Word Count:** 1076   **Line Count:** 00094

**Text:**

SPECIAL TO CANADIAN PACKAGING

If you're in the business of manufacturing a blood substitute product that ends up infused into a human body, product quality is understandably a paramount consideration.

And for Toronto-based Hemosol Inc., achieving that level of quality meant making a clear connection between product quality and the type of material used to package its rather unconventional product.

In its quest to maintain product stability and preserve product efficacy, Hemosol turned to a transparent flexible laminate that offered

the promise of the highest barrier levels. Manufactured by Rollprint Packaging Products of Addison, Ill., the company's newest laminate in its ClearFoil family of films - called ClearFoil SiOX-F - turned out to be just such a material.

"Hemoglobin products are very oxygen-sensitive. We had to find a packaging material that would keep the gas permeability to a minimum," explains Dr. Dirk Alkema, vice-president of manufacturing at Hemosol.

"The ClearFoil film meets our specifications for high oxygen and moisture barrier properties, while the clarity of the material maintains our product's visibility."

The development of blood substitute products has its roots in military research into overcoming the issues of blood availability and stability in the field.

In the mid-80s, privately-owned Hemosol was formed to commercialize a blood substitute technology based on research conducted at Canada's Department of Natural Defense.

Its flagship product - Hemolink - is manufactured from highly purified human hemoglobin and is currently undergoing four Phase II trials

in three countries - Canada, the U.S. and the U.K.

"The need for a blood substitute also arises from concerns about



viral contamination of the blood supply with HIV and Hepatitis, and even unknown viruses that are not currently screened for by the Red Cross or other blood collection agencies," notes Dr. Peter Wojciechowski, Hemosol's manager of process development.

"In addition, concerns of cross-matching blood types and periodic shortages of donated blood fuel the demand for alternatives to allogeneic or donated blood."

Hemosol packages Hemolink in an IV infusion bag that resembles those used for allogeneic blood. Originally, when Hemosol searched for an overpouch simply to maintain the cleanliness of the IV bag, it selected a nylon overpouch, which was fine for what at the time was produced primarily as a frozen product.

"We realized we could increase product shelf-life tremendously and simultaneously increase product storage temperatures if we improved the barrier properties of the overpouch," says special products manager Sam Teleki.

"We started analyzing the permeability of many different laminates from a variety of different manufacturers."

About a year ago, Hemosol learned of Rollprint's family of ClearFoil laminates - engineered to provide exceptionally high barrier levels in combination with good clarity qualities. While Rollprint offers many high-barrier laminates to match a wide variety of applications, Hemosol selected Rollprint's highest-barrier ClearFoil film in order to minimize gas permeability. This new, three-layer laminate uses ClearFoil SiOX-F material sandwiched between a 2.5-mm sealant layer and a 75-gauge oriented polypropylene (OPP) layer.

"We manufacture a highly purified blood product that carries oxygen," Alkema says. "To protect the efficacy of the product, we need to keep the gas permeability to a minimum."

The ClearFoil SiOX-F laminate also provides high moisture barrier that is of vital importance to Hemosol allowing water vapor permeability of only 0.02 grams per 100 square inches per day.

"Minimizing water vapor loss protects product concentration," Teleki

explains. "For example, if we produce a product with a 10-per cent concentration of hemoglobin, fill 100 milliliters into an IV bag, and then

we lose three milliliters of moisture during the shelf-life of the product,

we've just increased the product concentration to 10.3 per cent."

Compared to the shelf-life of allogeneic blood that is limited to less than 42 days, Hemolink packed in Rollprint's ClearFoil SiOX-F overpouch achieves tremendous improvements.

"We haven't finalized our data yet, but the shelf-life of the Hemolink product looks promising," Alkema notes. "We're projecting we have at least a two-year shelf-life at four degrees Celsius and at least one-year shelf-life at room temperature."

While high temperatures challenge the stability of all blood products, it is the lower temperatures that tend to challenge flexible films.

"Flex crack resistance becomes more difficult at cold temperatures because some plastics become very brittle. If the overpouch is punctured or cracked, we lose package integrity," Teleki notes.

"The flex crack characteristics of the ClearFoil laminate are good, even at very low temperatures. We should know, one of our products is stored at minus 80 degrees Celsius and the material is still pliable."

If high-level barrier was all Hemosol was interested in, it could have been satisfied with a foil pouch, but the company also hoped to offer a package with good clarity. The clarity of the ClearFoil SiOX-F laminate allows for the visual monitoring of the product and increases product acceptance.

"Clinicians are used to seeing blood in an IV bag. They visually inspect the blood, checking the color of the product as an indication of product quality. We wanted to offer our product in a similar package so people would be comfortable using it," Wojciechowski explains. "The clarity of the ClearFoil overpouch allows the clinicians to easily see the IV bag and the blood product inside."

With as many as seven companies racing to be the first to win FDA approval for a blood substitute product, Hemosol is continuously making concerted efforts to maximize product efficacy and safety.

"One thing that sets us apart is our process. We believe we have the most highly purified human hemoglobin and a superior stabilizing process that give us a longer circulating half-life," Alkema says. "Market demand projections for a blood substitute product are estimated at three million units per year in North America alone. We're hoping to be licensed and marketing the product by the year 2001. At that point, we would be handling much larger batch runs."

"We are a small company with a small production volume but a promising future. Rollprint's willingness to work with us to develop a new product is impressive," Alkema says. "We just asked for help finding a low gas permeable membrane and they went to work to identify the combination of laminates that would meet our needs. They're helping us to make the blood

supply safer, more economical, and easier to manage."

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**Special Features:** illustration; 1

**Company Names:** Hemosol Inc.--Products

**Descriptors:** Blood substitutes--Packaging; Blood products--Packaging; Packaging industry --Products

**Geographic Codes/Names:** 1USA United States

**SIC Codes:** 2836 Biological products exc. diagnostic; 2670 Misc. Converted Paper Products

**Event Codes/Names:** 460 Use of materials & supplies

**Product/Industry Names:** 2833440 (Synthetic Blood); 2649910 (Sterilized Medical Packaging)

**File Segment:** TI File 148

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13/9/16 (Item 2 from file: 149)

DIALOG(R)File 149: TGG Health&Wellness DB(SM)

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01641618 **Supplier Number:** 18748015 (THIS IS THE FULL TEXT )

**Blood substitute offers advantages. (experimental Hemolink, a red blood cell substitute from Hemosol Inc, does not possess the disadvantages of donated blood)(Brief Article)**

USA Today (Magazine) , v124 , n2609 , p13(1)

Feb ,

1996

**Document Type:** Brief Article **Publication Format:** Magazine/Journal

ISSN: 0161-7389

**Language:** English

**Record Type:** Fulltext **Target Audience:** Consumer

**Word Count:** 459 **Line Count:** 00041

**Text:**

Blood donated for transfusions has several drawbacks: it must be used within five or six weeks, might carry viruses such as HIV, and only can be given to patients with a compatible blood type. These and other problems result in periodic blood shortages. However, a red blood cell substitute without these flaws is going into human safety/efficacy trials early in 1996 and, if all goes well, could be available on the market by 1999.

An average adult has about five quarts of blood, encompassing a complex

mixture of red and white cells, plasma, and platelets. The red cells contain the oxygen-carrying molecule hemoglobin, which lies at the heart of the blood substitute being developed by Hemosol Inc., based in Etobicoke, Ont., Canada. Called Hemolink, it is made of chemically modified hemoglobin, derived from screened and tested blood that is outdated because it has been stored for more than six weeks.

The process takes the expired blood, separates out the red blood cells, and extracts the hemoglobin. That is more complicated than it sounds. "A red cell is not just a package of clean hemoglobin," notes Gord Adamson, a Hemosol scientist. "It contains about 90 different proteins." The company heats the hemoglobin to destroy any contaminating viruses that may have eluded the screening process conducted by collection agencies. Other remaining proteins are removed by a displacement chromatographic process that strips away blood-group antigens and other proteins, so Hemolink can be used by all patients regardless of blood type.

The purification steps make the likelihood of transmission of diseases such as AIDS and hepatitis virtually nil, according to Adamson. "The reason we say 'virtually' is because scientifically it is impossible to prove total absence of a virus." After purification, the free hemoglobin is cross-linked with oxidized raffinose, a sugar molecule. This improves its ability to deliver oxygen to tissue, stabilizes each hemoglobin molecule, and links together several such molecules so that they are large enough to circulate for extended periods.

Hemosol is working with two versions of Hemolink, one a fluid stored in a refrigerator and one frozen. Either formulation would be suitable for surgical applications. A long-term goal is to develop a freeze-dried formulation light enough to ship to remote depots - for use in disasters or military conflicts, for example - that could be reconstituted with sterile water on-site.

The substitute would avoid some of the costly problems associated with blood transfusions - such as transmission of disease (ranging from AIDS or hepatitis to a bacterial infection), mismatched blood (where the patient might have a reaction to antigens in the donor's blood that could be mild, such as a fever, or severe, resulting in death), or the delays in surgery brought about by blood shortages.

**Special Features:** illustration; photograph  
**Company Names:** Hemosol Inc.--Product development  
**Descriptors:** Blood substitutes--Innovations  
**File Segment:** MI File 47

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13/9/17 (Item 3 from file: 149)  
DIALOG(R)File 149: TGG Health&Wellness DB(SM)  
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01193508   **Supplier Number:** 08093457 (THIS IS THE FULL TEXT )  
**Synthesis of functional human hemoglobin in transgenic mice.**

Behringer, Richard R.; Ryan, Thomas M.; Reilly, Michael P.; Asakura, Toshio ; Palmiter, Richard D.; Brinster, Ralph L.; Townes, Tim M.  
Science , v245 , n4921 , p971(3)  
Sept 1 ,  
1989

**Publication Format:** Magazine/Journal  
ISSN: 0036-8075  
**Language:** English  
**Record Type:** Fulltext **Target Audience:** Academic  
**Word Count:** 2144   **Line Count:** 00213

**Text:**

Synthesis of Functional Human Hemoglobin in Transgenic Mice

CORRECTLY REGULATED EXPRESSION of human [beta]-globin genes in transgenic mice is well documented [1, 2]. The human gene is expressed only in adult erythroid tissue and, in some animals with relatively high transgene copy numbers, the level of human [beta]-globin mRNA is equivalent to endogenous mouse [beta]-globin mRNA. Analysis of constructs with [beta]-globin gene fragments inserted upstream of a reporter gene demonstrate that sequences located immediately upstream, within and downstream of the gene contribute to the correct temporal and tissue specific expression [3]. Sequences located 50 kb upstream of the [beta]-globin gene also have an effect on globin gene expression [4-8]. When these sequences that contain erythroid-specific, DNase I super-hypersensitive (HS) sites are fused upstream of the human [beta]-globin gene and injected into fertilized mouse eggs, large amounts of human [beta]-globin mRNA are synthesized in virtually all transgenic mice that develop [5, 7]. These experiments

suggest that the super-hypersensitive sites define locus activation regions

that "open" a large chromosomal domain for expression specifically in erythroid cells and dramatically enhance globin gene expression.

The human [alpha] 1-globin gene is also expressed at high levels in

erythroid tissue of transgenic mice when the injected gene is flanked by

super-hypersensitive sites from the human [beta]-globin locus [8]. Thus a

complete human hemoglobin could be synthesized in mice if human [alpha]-

and [beta]-globin gene constructs were coinjected into fertilized eggs.

Previous studies demonstrated that two of the five HS sites in the [beta]-globin locus were sufficient for high-level expression [7, 8].

Therefore, we inserted HS I and II (a 12.9-kb Mlu I--Cla I fragment) upstream of the human [alpha] 1- and [beta]-globin genes (Fig. 1) and coinjected equimolar amounts of these constructs into fertilized mouse eggs

[9]. The eggs were transferred into the oviducts of pseudopregnant foster

mothers, and seven transgenic mouse lines were established from founder animals that contained intact copies of the injected fragments. Total RNA

from ten tissues of adult progeny were then analyzed for correctly initiated human [alpha]-, human [beta]-, mouse [alpha]-, and mouse [beta]-globin mRNA by primer extension [10] (Fig. 2A). Human [alpha]- and

[beta]-globin transgenes were expressed only in blood and spleen, which are

both erythroid tissues in mice; detection in the lung is the result of blood contamination [11] because both human and mouse [alpha]- and [beta]-

globin mRNA are observed in this nonerythroid tissue. Human [alpha]- and

[beta]-globin mRNA levels in blood, as measured by solution hybridization,

were 100% and 120% of endogenous mouse [beta]-globin mRNA, respectively.

Therefore, erythroid-specific, human [alpha]- and [beta]-globin gene expression can be achieved in adult transgenic mice after coinjection of

[alpha]- and [beta]-globin constructs that contain HS I and II.

To determine whether complete human hemoglobins were formed, we separated hemolysates [12] of the blood of animals from two different transgenic lines by non-denaturing isoelectric focusing (IEF) (Fig. 2B).

The

first lane is a mouse control and the last lane is a normal human sample.

The predominant band in each of the control is the major adult hemoglobin;

mouse [[alpha].sub.2.[beta].sub.2] or human

[[alpha].sub.2.[beta].sub.2]

respectively. In both transgenic mouse samples 5394 and 5393, bands that

run at the sample pI as human Hb A ([h[alpha].sub.2.h[beta].sub.2]) and

mouse hemoglobin ( $[m[\alpha].\text{sub.2}.m[\beta].\text{sub.2}]$ ) are observed. In addition to human and mouse hemoglobins, two other major bands were observed in both transgenic samples. To determine the composition of these bands and to confirm the human and mouse hemoglobins, the four bands in sample 5393 were exercised from the gel and analyzed on a denaturing cellulose acetate strip [13] (Fig. 2C). Control lysates of mouse, human, and 5393 blood samples were separated in lanes on the left. Mouse  $[\alpha]$ - and  $[\beta]$ -globin polypeptides, as well as human  $[\alpha]$ - and  $[\beta]$ -globin polypeptides, were well separated on this strip. Sample 5393 contained all four polypeptides; the human  $[\alpha]$ - and  $[\beta]$ -globin polypeptides were 110% and 106% of the amounts of mouse  $[\alpha]$ - and  $[\beta]$ -globin, by densitometric analysis. The top band (band 1) of sample 5393 in Fig. 2B is composed of human  $[\alpha]$ - and mouse  $[\beta]$ -globin chains. The second band is mouse  $[\alpha]$ - and mouse  $[\beta]$ -globin and the third band is human  $[\alpha]$ - and  $[\beta]$ -globin as expected. The polypeptides composing band 4 in Fig. 2B are barely visible in Fig. 2C but are clearly mouse  $[\alpha]$ - and human  $[\beta]$ -globin. Therefore, normal amounts of human hemoglobin can be synthesized in adult mice, and multiple combinations of globin polypeptides are possible [see note [14]].

The functional properties of human, mouse, and hybrid hemoglobins synthesized by transgenic mice were assessed by determination of oxygen equilibrium curves (OEC) and by calculation of  $[P.\text{sub.50}]$  values. The  $[P.\text{sub.50}]$  is the partial pressure at which hemoglobin is half saturated with oxygen and is inversely related to hemoglobin oxygen affinity. All four hemoglobins described above were purified by preparative IEF [15] and the OEC for each was determined [16] (Fig. 3). The OEC were normal, sigmoid-shaped, and demonstrate that all four hemoglobins bind oxygen cooperatively. The  $[P.\text{sub.50}]$  of human hemoglobin synthesized by transgenic mice is 8.0 mmHg, which is identical to the  $[P.\text{sub.50}]$  of native human Hb A. Interestingly, the oxygen affinities of the two hybrid tetramers differ significantly from human and mouse hemoglobins. The  $[h[\alpha].\text{sub.2}.m[\beta].\text{sub.2}]$  hybrid has an extremely low  $[O.\text{sub.2}]$  affinity; the  $[P.\text{sub.50}]$  is 15.7 mmHg. In contrast, the  $[O.\text{sub.2}]$  affinity for  $[m[\alpha].\text{sub.2}.h[\beta].\text{sub.2}]$  is extremely high; the  $[P.\text{sub.50}]$  for this hemoglobin is 4.7 mmHg [17].

Finally, the hematological values of six transgenic progeny were determined and compared to five normal animals. Red blood cell counts and hematocrits for transgenic animals were normal and, interestingly, the

values for hemoglobin and mean corpuscular volume were in the normal range. Consequently, the calculated values of mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration (MCHC) for transgenic animals were normal. Thus the total hemoglobin concentration in transgenic erythrocytes is not increased even though reticulocytes contain 100% more globin mRNA [18]. Therefore, to maintain normal MCHC, all globin mRNAs are either translated at reduced rates or [alpha]- and [beta]-globin polypeptides are less stable. Another possibility is that globin synthesis ceases when the maximum intracellular concentration of hemoglobin is attained. If the rate of globin synthesis is normal, then a full complement of hemoglobin could be synthesized in half the time leading to faster maturation of reticulocytes.

In summary, the results presented demonstrate that high levels of human [alpha]- and [beta]-globin mRNA can be coexpressed in mice. The transgenes are expressed specifically in erythroid tissue and levels of human hemoglobin equivalent to mouse hemoglobin can be achieved. In addition, the human hemoglobin produced in these mice is fully functional and the transgenic animals are phenotypically normal. These results provide a solid foundation for the production of transgenic mice that synthesize high levels of other human hemoglobins. We have initiated studies to synthesize high levels of human sickle hemoglobin in transgenic mice in an attempt to produce a mouse model of sickle cell disease. Although sickle cell anemia was the first disease to be understood at the molecular level [19], there is still no cure or adequate treatment. If a transgenic mouse model can be developed, new drug therapies and even gene therapies could be tested. Once perfected in model systems, protocols that are safe and effective for humans could be developed.

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[10] Adult animals were made anemic with phenylhydrazine [20] to induce reticulocytosis, anesthetized, perfused [11], and tissues were removed. Total RNA was prepared from frozen tissue [*Anal. Biochem.* 162, 156

(1987)] with the following modification. The final RNA pellets were resuspended in a solution containing 1.0% SDS, proteinase K (100 mg/ml), 25

mM NaCl, 1.0 mM EDTA, and 10 mM tris-HCl pH 7.5. After digestion for 3 hours at 50 [degrees]C, the samples were extracted with phenol/chloroform, chloroform, and ethanol precipitated.

[11] Animals were perfused by cutting the right atrium and injecting phosphate-buffered saline into the left ventricle. The lung is not perfused

in this procedure and, therefore, is contaminated with blood.

[12] Blood cells were washed twice with saline and lysed in a volume

of water equal to the cell pellet. One-fourth volume of carbon tetrachloride was mixed with the hemolysate, and cell membranes were extracted by brief vortexing and microcentrifugation. The aqueous phase was

removed and frozen at 20 [degrees]C. Samples were subsequently thawed, diluted with an equal volume of 0.05% KCN, and separated on an agarose isoelectric focusing gel (Resolve-Hb, Isolabs Inc., Akron, Ohio) according

to the manufacturer's specifications. After focusing, proteins were fixed

in the gel with 10% trichloroacetic acid for 10 min. The gel was then rinsed for 1 hour with water, dried, and hemoglobin bands were visualized

without staining.

[13] Hemoglobin bands were cut out of the agarose IEF gel and eluted

in water for 1 hour at room temperature. After dialysing against water overnight at room temperature, the samples were lyophilized and resuspended

in water. Equal volumes of sample (purified hemoglobin or whole

hemolysate), alkaline-urea buffer (6.0M urea, 15 mM boric acid, 0.5 mM EDTA, 25 mM tris-HCl, pH 8.6), and [beta]-mercaptoethanol were mixed and an aliquot was loaded onto a cellulose acetate strip (Gelman) that had been soaked overnight in alkaline-urea buffer. The samples were then electrophoresed for 1 hour at 19 V in alkaline-urea buffer. Proteins were subsequently stained with 0.5% imido black in methanol: acetic acid (45:10). The strips were destained in methanol: acetic acid (47.5:5), dried, and photographed.

[14] Although only four hemoglobin bands are observed on the IEF gel in Fig. 2B, nine hemoglobins representing all possible combinations of mouse and human [alpha]- and [beta]-globin polypeptides probably exist inside the cell. During electrophoresis oxy-hemoglobin tetramers ( $[[\alpha]_{\text{sub.2.}}[\beta]_{\text{sub.2.}}]$ ) dissociate into dimers ( $[[\alpha]_{\text{sub.1.}}[\beta]_{\text{sub.1.}}]$ ) that are separated by charge differences. Therefore, hemoglobin tetramers composed of dimers of unlike charge are not detected [21].

[15] Mouse, human, and hybrid hemoglobins synthesized by transgenic mice were separated by preparative IEF on 4.0% acrylamide gels containing 2.0% Pharmalyte pH 5 to 8. Each of the four bands was sliced from the gel, homogenized, and the hemoglobin was eluted in 0.1M potassium phosphate buffer. The isolated fractions were concentrated with Amicon filters (YM 10).

[16] Hemoglobins were maintained in the carbon monoxide (CO) form during separation and concentration procedures to avoid auto-oxidation. Prior to functional studies the hemoglobins were converted to the oxy-state by photolysis and vacuum removal of CO. The oxygen equilibrium curve of each hemoglobin fraction was determined using a Hemox Analyzer (TCS, Southhampton, PA) in 0.1M potassium phosphate buffer, pH 7.0 at 20[degrees]C [22]. All samples were analyzed four times and the curves were drawn in continuous mode. The maximum error of measurement of the  $[P_{\text{sub.50}}]$  values is [+ or -] 1 mmHg [Crit. Care Med. 7, 391 (1979)].

[17] OEC of whole blood and unfractionated hemolysates from transgenic mice were also determined and compared to mouse and human controls. The curve for whole blood of 5393 transgenic progeny is virtually identical to the mouse control, while the curve for an unfractionated transgenic hemolysate is shifted to the left of the mouse hemolysate control. The left shift of the transgenic hemolysate OEC can be attributed to the presence of high-affinity hybrid and human hemoglobin species. The similarity of the whole blood OEC for transgenic and control mice may be due to adaptive responses, such as an increase in allosteric effectors of

oxygen affinity, in the transgenic mice.

[18] Quantitative solution hybridizations of blood RNA from the seven transgenic lines indicate that mouse [alpha]- and [beta]-globin mRNA levels

(picograms of total RNA per microgram) are not decreased in mice expressing

high levels of human [alpha] and [beta]-globin mRNA.

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[23] We thank N. Martin, J. Askins, and M. Avarbock for excellent technical assistance, J. Prchal for providing human reticulocyte RNA, K.

Hall for instructions on electrophoresis of hemoglobins on denaturing cellulose acetate strip, and J. Engler for synthesizing the human [alpha]-,

human [beta]-, mouse [alpha]-, and mouse [beta]-globin oligonucleotides.

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**Captions:** HS I,II alpha-globin and HS I,II beta-globin gene constructs. (chart); Expression of human alpha- and beta-globin genes in transgenic mice. (chart); Oxygen equilibrium curves of hemoglobins. (graph)

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**Special Features:** illustration; chart; graph

**Descriptors:** Mice as laboratory animals--Research; Gene expression--Research; Hemoglobinopathy--Models; Genetic transformation--Research; Hemoglobin-- Research

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**Dialog eLink:**

**ISPTO Full Text Retrieval Options**

13/9/18 (Item 1 from file: 162)

DIALOG(R)File 162: Global Health

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0004754137 **CAB Accession Number:** 20002007317

**KEMRI Hep-cell II hepatitis B surface antigen screening kit.**

Okoth, F. A.; Kaiguri, P. M.; Mathenge, E.; Tuei, J.; Muchiri, S.; Owino, N.; Kamau, G.; Kulundu, J.; Njuguna, A.; Tukei, P. M.; Yano, M.; Naruse, T.

Virus Research Centre, Kenya Medical Research Institute, P.O. Box 54628, Nairobi, Kenya.

East African Medical Journal vol. 76 ( 9 ): p.530-532

**Publication Year:** 1999

**ISSN:** 0012-835X

**Language:** English **Record Type:** Abstract

**Document Type:** Journal article

A study was conducted at the Centre for Virus Research, Kenya Medical Research Institute (KEMRI) in Nairobi to produce a hepatitis B surface antigen (HBsAg) kit locally to screen donated and patient blood samples in Kenya. Purified HBsAg from plasma of carriers obtained from national Public Health Laboratories Services was used to immunize guineapigs to produce anti-HB antibody. The anti-Hbs was then used to sensitize sheep rbc. The final product was freeze dried (lyophilized) and its sensitivity and specificity was compared with other commercial kits. The sensitivity and specificity of KEMRI Hep-cell II was 98% and 99%, respectively. The kit was stable and potent for one year whether kept at 4 or 37(deg)C or at room temperature. It is concluded that KEMRI Hep-cell II can be successfully produced locally, and that its sensitivity and specificity is comparable to other commercial kits. The kit requires only a simple apparatus to carry out the test hence it can be used anywhere in Kenya. It is also cheap and affordable. 4 ref.

**Descriptors:** antigens; detection; diagnosis; diagnostic techniques; hepatitis B; human diseases; passive haemagglutination; screening

**Identifiers:** antigenicity; efficacy; immunogens; passive hemagglutination; screening tests

**Organism Descriptors:** hepatitis B virus; man

**Geographic Names:** Kenya

**Broader Terms:** Hepadnaviridae; DNA Reverse Transcribing Viruses; viruses; Homo; Hominidae; Primates; mammals; vertebrates; Chordata; animals; eukaryotes; East Africa; Africa South of Sahara; Africa; Developing Countries; ACP Countries; Commonwealth of Nations; Anglophone Africa

**CABICodes:** Prion, Viral, Bacterial and Fungal Pathogens of Humans, (New March

2000) (VV210); Diagnosis of Human Disease, (New March 2000) (VV720); Techniques and Methodology (ZZ900)

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**Dialog eLink:**

**USPTO Full Text Retrieval Options**

13/9/19 (Item 1 from file: 444)

DIALOG(R)File 444: New England Journal of Med.

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00103092

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### **Elevated Fetal Hemoglobin Levels in Sudden Infant Death Syndrome (Original Article)**

Giulian, Gary G., B.A.; Gilbert, Enid F.; Moss, Richard L., Ph.D.

The New England Journal of Medicine

April 30 , 1987 ; 316 (18),pp 1122-1126

**Line Count:** 00337      **Word Count:** 04654

**ISSN:** 0028-4793

#### **Abstract**

The cause of sudden infant death syndrome (SIDS) is unknown, although deficits in cardiopulmonary function and central respiratory control have been suggested as possible mechanisms of the disorder. In this study, we tested the hypothesis that SIDS is associated with a delay in the maturation of hematopoiesis. Prolonged elevation in the levels of fetal hemoglobin (hemoglobin F) in infants with SIDS could denote a compromised delivery of oxygen to sensitive tissue sites. Normally, hemoglobin F ( $\alpha_2\gamma_2$ ) is largely replaced by adult hemoglobin, hemoglobin A ( $\alpha_2\beta_2$ ), during the first six months after birth.

Using an isoelectric-focusing procedure for measuring stable hemoglobin subunits, we quantitated the levels of hemoglobin F in blood samples from 59 patients with SIDS and 40 controls (32 living and 8 dead) matched for postconceptional age. The level of hemoglobin F in the population with SIDS was significantly higher than that in the controls in the age range tested (39 to 75 weeks); the mean ( $\pm$  SEM) proportion of hemoglobin F was  $63.2 \pm 3.6$  percent in the group with SIDS, as compared with  $48.1 \pm 5.0$  percent in the controls ( $P < 0.025$ ). The difference in hemoglobin F levels was most pronounced 50 weeks after conception: the proportion of hemoglobin F in the 37 patients with SIDS with a postconceptional age of more than 50 weeks was  $47.4 \pm 3.6$  percent, as compared with  $18.8 \pm 3.1$  percent in the 19 controls of that age ( $P < 0.0005$ ).

We conclude that hemoglobin F is a useful postmortem marker for the population with SIDS that we studied and that it may have value as a prospective marker for some infants at risk for SIDS. (N Engl J Med 1987; 316:1122-6).

**Text:**

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Supported in part by grants from local Wisconsin chapters of the National Sudden Infant Death Syndrome Foundation and by a grant (HL25861) from the National Institutes of Health.

SUDDEN infant death syndrome (SIDS) is responsible for approximately 2 deaths per 1000 live births in the United States, resulting in 7500 to 10,000 deaths annually. One of the most striking features of the syndrome is its age-related pattern; the incidence of SIDS peaks at two to four months after delivery, and it is rare after nine months.

Research into specific mechanisms frequently suggests an association between SIDS and cardiopulmonary deficiencies, defective central respiratory control, or both (Ref. 1-4).

This study was undertaken to determine whether levels of fetal hemoglobin (hemoglobin F) are elevated in patients with SIDS as compared with the levels in age-matched controls. Elevated levels of hemoglobin F at birth have previously been linked to chronic maternal anoxia (heart failure, severe bronchial asthma, and severe anemia), (Ref. 5) intrauterine growth retardation, (Ref. 6) placental insufficiency, (Ref. 7) prematurity, (Ref. 8) and maternal diabetes (Ref. 9). By eliminating (at autopsy) known clinical conditions (Ref. 10,11) associated with sustained elevations in hemoglobin F apparent in older persons (i.e., >1 month), such as sickle cell disease, hereditary persistence of fetal hemoglobin, thalassemia, hypoplastic anemia, leukemia, and trisomy 13, we found that hemoglobin F was substantially increased in the majority of patients with SIDS. Our finding was most clearly demonstrated in patients beyond 50 weeks of postconceptional age, in whom the elevation of hemoglobin F levels relative to the control values was the most pronounced.

**Methods****Sample Population and Standards**

Blood samples were collected at autopsies in Wisconsin and Minnesota during a five-year period (1981-1986). In all cases of death from SIDS or other known causes, complete autopsies were performed by pediatric pathologists at three centers -- the Marshfield Clinic, Marshfield, Wis. (n = 9), Minneapolis Children's Medical Center (n = 16), and the University of Wisconsin Hospital and Clinics, Madison (n = 42). Control samples were collected from normal living infants at Madison General Hospital (n = 32). All samples were collected and all tests were run under a protocol reviewed and approved by the University of Wisconsin-Madison Human Subjects Committee. We are reporting results from 59 patients with SIDS and 40 controls of comparable ages, including normal living infants (term and preterm) and 8 autopsy controls in which the cause of death was known. The autopsy findings in the controls included bronchopneumonia (n = 3), trauma (n = 3), acute aspiration pneumonia (n = 1), and the Budd-Chiari syndrome (n = 1). We also tested approximately 70 cord-blood samples (Lancaster Hospital, Lancaster, Wis., and Madison General Hospital) with regard to normal adult hemoglobin, purified globins, and commercial standards (Isolab, Akron, Ohio, and Gelman Scientific, Ann Arbor, Mich.).

Determination of Hemoglobin F at Autopsy

Whole blood (1 to 3 ml) was collected at autopsy through a heart puncture and was stored at 4 degreesC in EDTA-containing sterile vacuum tubes. Control samples (25 to 100 microliter) from living infants were collected by venous puncture and loaded into 500-microliter microfuge tubes containing 0.2 mg of Na(sub 2)EDTA in 20-microliter sterile deionized water and stored at 4 degreesC. The globin analysis was successfully used on whole blood, hemolysates, frozen blood, dried blood, and lyophilized standards. The total hemoglobin concentration was determined spectrophotometrically at 540 nm after conversion of hemolysate samples to cyanmethemoglobin (Data Medical Associates, Arlington, Tex.).

The percentage of hemoglobin F (relative to hemoglobin A) was determined by hemoglobin-subunit analysis with use of a high-voltage vertical-slab isoelectric focusing procedure (Ref. 12). Samples were mixed with a sample buffer that contained 8 M urea, 15 percent (vol/vol) glycerol, 5 percent (wt/vol) sorbitol, 2 percent (vol/vol) Triton X-100, an ampholyte concentration described previously, (Ref. 12) and 15 mM dithiothreitol. The liquid blood samples (3 microliter) were diluted to 1:10 with sample buffer and then incubated at 37 degreesC for 15 minutes, after which 1 to 3 microliter was loaded onto the acidic end of the 5.5 percent (wt/vol) polyacrylamide gel prepared with 8 M urea, 15 percent (vol/vol) glycerol, 5 percent (wt/vol) sorbitol, 1.5 percent (wt/vol) ampholyte (pH 6 to 8), 0.75 percent (wt/vol) ampholyte (pH 4 to 6), 0.75 percent (wt/vol) ampholyte (pH 5 to 7), and 0.30 percent (wt/vol) ampholyte (pH 3.5 to 10). The gels were run on an SE600 electrophoresis cell (Hoefer Scientific Instruments, San Francisco). After focusing, the gel was fixed and stained with Coomassie R-250, dried between layers of cellophane and Mylar, (Ref. 13) and scanned with a BioMed 504XL scanner (BioMed Instruments, Fullerton, Calif.). The areas under the peaks were digitally integrated to determine the relative amounts of each globin chain present. The percentage of hemoglobin F was determined by calculating the ratio of the sum of the two gamma peaks ((sup A)gamma and (sup G)gamma) over the sum of the gamma and beta peaks. Since the alpha-globin chain normally constitutes a fixed fraction of total hemoglobin at all ages, this was not included in the calculation. Dilution studies (data not shown) demonstrated a linear Coomassie staining range of approximately 0.1 to 2.5 microgram of protein for both the gamma and beta chains.

#### Analysis of Data

Eighteen samples were run simultaneously on the same gel, and the stained gels were analyzed for hemoglobin F content by persons who did not know the age of the infant or the cause of death (if any). Only after the hemoglobin F was measured was the sample matched with the age and outcome. The hemoglobin F values in the patients with SIDS and the age-matched controls were compared with use of Student's unpaired two-tailed t-test.

#### Results

Figure 1 demonstrates the accuracy of the hemoglobin F determination by means of hemoglobin-subunit analysis. Known relative amounts of hemoglobin F and hemoglobin A were compared for their relative proportions of gamma- and beta-globin chains as measured with the isoelectric-focusing protocol. Each of the points in Figure 1 represents the mean value from analyses of three separate gels, and the data showed good linearity ( $r = 0.9917$ ) between the proportion of gamma-globin chain and the total hemoglobin F between 0 and 97.5 percent. The use of subunit analysis of denatured samples eliminated

the problems associated with heterogeneity in the charge of the heme ring in native hemoglobin tetramers. \*Figure 1. Determination of Levels of Hemoglobin F (HbF) with Hemoglobin-Subunit Analysis \*. \*\*FIGURE OMITTED\*\*

The results of an analysis of a representative gel are shown in Figure 2. Lane A contains a hemoglobin A and hemoglobin S standard with both the beta and beta (sup s) (sickle) isoforms, whereas B and C contain mixed hemoglobin F and hemoglobin A standards. The standards served as internal controls, with Lane B containing a high proportion of hemoglobin F (85 percent) and Lane C a low proportion (10 percent). Lanes 1 to 4 demonstrate the globin profiles of living controls matched for the postconceptional ages of 51 and 63 weeks (Lanes 1 and 3) with infants with SIDS (Lanes 2 and 4). The hemoglobin F levels were substantially higher in the blood from the patients with SIDS than in the blood from the controls at both 51 and 63 weeks of postconceptional age (Fig. 3). The (sup G)gamma/(sup A)gamma ratios were calculated from the scans shown in Figure 3, as follows: Lane 1, 2.2; Lane 2, 2.5; Lane 3, 0.7; and Lane 4, 1.8. Previous studies have shown that the ratio is normally 3:1 at birth and approximately 2:3 at six months of age (Ref. 14). The control samples (1 and 3 in Fig. 3) had normal (sup G)gamma/(sup A)gamma ratios for their respective ages; however, although the patients with SIDS (2 and 4) had normal ratios for the percentage of hemoglobin F present, these ratios were elevated for their postconceptional ages. \*Figure 2. Electrophoretic Separation of Hemoglobin Subunits. An isoelectric-focusing gel of blood samples was loaded from the acidic side to a total of 0.5 to 2.5 microgram of globin per band. Lanes A to C contained hemoglobin standards hemoglobins A and S (AS) and hemoglobins A and F (AF). Note that although our study population was predominantly white (Table 1), the gel-analysis procedure used in this study can resolve hemoglobin F in the presence of beta (sup s). Lanes 1 to 4 contain samples from age-matched infants with SIDS and controls \*. \*\*FIGURE OMITTED\*\* \*Table 1. Characteristics of the Study Population \*. \*\*TABLE OMITTED\*\* \*Figure 3. Densitometric Scans of Globin Profile. Densitometric scans of Lanes 1 to 4 of the gel in Figure 2 are shown. The values in each panel represent the percentage of fetal hemoglobin in the corresponding blood sample \*. \*\*FIGURE OMITTED\*\*

The results of these analyses are summarized in Figure 4, in which the percentage of hemoglobin F in the SIDS and control groups is plotted against increasing postconceptional age. Each point represents the result from an individual blood sample and is the mean of three completely separate hemoglobin F determinations (all within a 10 percent range). All samples (in both control and SIDS groups) were from infants born at least two weeks before the sample was taken; 10 infants in the control group had been born 4 to 14 weeks prematurely (Table 1). The mean (+/- 2 SD) value for the normal decline in hemoglobin F with increasing age (Fig. 4) was derived from 432 different determinations of the percentage of hemoglobin F with use of alkali denaturation, (Ref. 59) Fe labeling, and globin analysis (Ref. 15-18). We assumed a term delivery to be one that occurred at least 39 weeks after conception. \*Table 1. Characteristics of the Study Population \*. \*\*TABLE OMITTED\*\* \*Figure 4. Percentage of Hemoglobin F, According to Postconceptional Age in Samples from Patients with SIDS and Controls. The solid line denotes the calculated mean value for the normal decline in hemoglobin F with increasing age, and the broken lines +/- 2 SD. Autopsy data indicated by x are from forensic cases involving homicide \*. \*\*FIGURE OMITTED\*\*



The data on the infants with SIDS and the controls are summarized in Table 2 according to age group (less than 50 weeks -- below the midpoint of the normal steep decline in hemoglobin F Fig. 4] -- and more than 50 weeks) and in the total population (39 to 75 weeks). The hemoglobin F levels in each of the populations with SIDS were significantly elevated as compared with those in our controls and the published normal ranges, particularly those after 50 weeks of postconceptional age. \*Table 2. Levels of Hemoglobin F in Subjects in Three Postconceptional Age Groups \*. \*\*TABLE OMITTED\*\* \*Figure 4. Percentage of Hemoglobin F, According to Postconceptional Age in Samples from Patients with SIDS and Controls. The solid line denotes the calculated mean value for the normal decline in hemoglobin F with increasing age, and the broken lines +/- 2 SD. Autopsy data indicated by x are from forensic cases involving homicide \*. \*\*FIGURE OMITTED\*\*

## Discussion

Investigations of possible mechanisms for SIDS have failed to provide a single hypothesis that is consistent with the diverse findings at autopsy. Steinschneider (Ref. 19) proposed that hypoventilation is a possible risk factor for SIDS, and Naeye (Ref. 20,21) subsequently found evidence of chronic hypoxemia at autopsy. Of the seven tissue markers that have been widely studied in connection with SIDS, at least three appear to have a strong association with the syndrome (Ref. 3): an increase in periadrenal brown fat, hematopoiesis in the liver, and brain-stem astrogliosis. Even these findings are somewhat controversial, (Ref. 2,22) partly because of the subjectivity involved in identifying pathological indexes and postmortem changes in tissue samples and in the selection of appropriate controls. Epidemiologic studies (Ref. 23-26) of SIDS suggest an association with low birth weight, prematurity, retarded growth development, and maternal smoking.

Although the underlying mechanisms for our findings are not known, the population of patients with SIDS that we studied had marked elevations in hemoglobin F. The reason for the abnormal persistence of hemoglobin F is uncertain, but it may be explained on the basis of a delay in the replacement of hemoglobin F by hemoglobin A. Naeye's evidence (Ref. 20) for residual liver hematopoiesis in patients with SIDS may indeed be indicative of delayed hematopoietic development, although the switch from hemoglobin F to hemoglobin A normally occurs independently of the site of hematopoiesis (Ref. 14,27). Given that the half-life of circulating fetal erythrocytes is approximately 70 days, (Ref. 27) the observed elevation in hemoglobin F in the blood of patients with SIDS would appear to be part of a process that occurs over several weeks rather than hours or minutes. This is consistent with the suggestion that chronic conditions may underlie SIDS, (Ref. 28) but it certainly does not exclude the possibility that the final event is acute obstructive hypoxia (Ref. 29-31).

Our populations were matched for postconceptional age, since the normal decline in hemoglobin F is based on the total developmental age. The majority of our patients with SIDS were delivered at or near term (Table 1); thus, consideration of gestational age would not have significantly altered the distribution of the data. Only three of our control samples were from infants who died as a result of trauma, but all the control values for hemoglobin F were within the established normal range (+/- 2 SD) when postconceptional age was taken into account. Neither our patients with SIDS nor our controls had any known hematologic disorders. Indeed, conditions that may result in

abnormally elevated levels of hemoglobin F after approximately 50 weeks, such as thalassemias, sickle cell disease, aplastic anemia, hereditary persistence of fetal hemoglobin, and leukemia, (Ref. 11) do not appear to be associated with SIDS. \*Table 1. Characteristics of the Study Population \*. \*\*TABLE OMITTED\*\*

The peak incidence of SIDS occurs among infants two to four months old -- an age at which total hemoglobin levels are normally minimal because of infant anemia (Ref. 14,27). Brown et al. (Ref. 32) have concluded that elevated hemoglobin F levels in preterm infants are of concern only under stressful conditions. Thus, an elevated hemoglobin F level and the coincident normal anemia could be benign unless there is an acute episode during which the combination of these conditions would limit oxygen tension. Consistent with this idea, the period during which the hemoglobin concentration is minimal is well correlated in time with the peak incidence of SIDS (Fig. 5), (Ref. 33) with preterm infants (who are at higher risk for SIDS) having a lower total hemoglobin level two to four months after delivery (Ref. 27). \*Figure 5. Mean Total Hemoglobin (Hb) Level and the Occurrence of SIDS, According to Post-Delivery Age. The normal period of infant anemia occurs simultaneously with the peak incidence of SIDS. Preterm infants with a higher proportion of hemoglobin F also tend to have a more severe anemia after delivery, and as a group, they are at higher risk for SIDS. Total hemoglobin concentration can be measured only in living infants. Data were derived from Naeye (Ref. 33) and Dallman (Ref. 27) \*. \*\*FIGURE OMITTED\*\*

An earlier brief report (Ref. 34) indicated that there was no difference in hemoglobin F levels between subjects with SIDS and controls. Since a full report has not yet been published, we are unable to assess possible reasons for the apparent discrepancy with our results. However, it is important to note that many commonly used methods of determining hemoglobin F content in fresh blood do not appear to be appropriate for autopsy samples. Early in the present study, both the alkali-denaturation method and native hemoglobin separation procedures were abandoned because of poor reproducibility due to the variable hemolysis of whole blood samples and oxidation of the heme ring. Furthermore, the alkali-denaturation method is also not recommended on any test material containing more than 40 percent hemoglobin F (Ref. 35) without previous dilution with hemoglobin A, (Ref. 17) since the assessment will otherwise appear to underestimate the hemoglobin F content (Ref. 18,35).

In summary, a randomly selected population of infants with SIDS diagnosed by means of a complete autopsy was found to have elevated levels of hemoglobin F relative to those in age-matched controls. Our interpretation of this finding is that infants with SIDS are characterized by a marked delay in the switch from hemoglobin F to hemoglobin A -- a phenomenon that may reflect an underlying chronic condition. Although the conditions that predispose to a SIDS episode remain elusive, the finding of an elevation in hemoglobin F level may be useful as a diagnostic postmortem indicator for SIDS and may have value as a prospective marker for some infants at risk for SIDS, especially those beyond 50 weeks of postconceptional age.

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